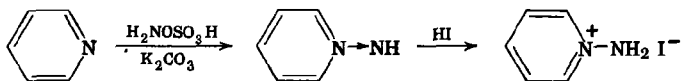


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1-AMINOPYRIDINIUM IODIDE

(Pyridinium, 1-amino-, iodide)



Submitted by R. GÖSL and A. MEUWSEN.¹

Checked by N. A. FEDORUK and V. BOEKELHEIDE.

1. Procedure

To a freshly prepared solution of 11.3 g. (0.10 mole) of hydroxylamine-O-sulfonic acid² (Note 1) in 64 ml. of cold water there is added 24 ml. (24 g., 0.30 mole) of pyridine (Note 2). The mixture is heated at about 90° on a steam bath for 20 minutes. It is then cooled to room temperature with stirring, and 13.8 g. (0.10 mole) of potassium carbonate is added. The water and excess pyridine are removed from the mixture by heating it at 30–40° in a rotatory evaporator in conjunction with a water aspirator. The residue is treated with 120 ml. of ethanol, and the insoluble precipitate of potassium sulfate is removed by filtration.

Fourteen milliliters (22 g., 0.10 mole) of 57% hydriodic acid is added to the filtrate, and the resulting solution is stored at –20° for 1 hour (Note 3). The solid that separates is collected; weight 15.5–17.5 g. Recrystallization of this solid from about 100 ml. of absolute ethanol gives 14–16 g. (63–72%) of 1-aminopyridinium iodide as almost-white crystals, m.p. 160–162° (Note 4).

2. Notes

1. Because aqueous solutions of hydroxylamine-O-sulfonic acid are not very stable, it is very important to use freshly prepared solutions. The purity of hydroxylamine-O-sulfonic acid should be checked by iodometric titration. If it is less than 85–

90% pure, the yield of 1-aminopyridinium iodide will suffer. The acid can be purified by dissolving it in an equal weight of water and then precipitating it by stirring 7 volumes of acetic acid into the solution.

2. The pyridine was distilled before use. When the conversion is carried out in the presence of potassium carbonate using an equimolar amount of pyridine instead of an excess, the yields obtained are 20–30% lower.³

3. The temperature is kept at -20° or lower by a bath of dry ice and methanol. If the temperature rises above -20° , an appreciable quantity of 1-aminopyridinium iodide may redissolve and be lost.

4. The melting point recorded for 1-aminopyridinium iodide is $161\text{--}162^{\circ}$.³

3. Methods of Preparation

The formation of 1-aminopyridinium chloride has been accomplished by the acid hydrolysis of N-(*p*-acetaminobenzene-sulfonimido)pyridine.⁴ Also, the rearrangement of a substituted diazepine has been observed to give a 1-aminopyridine derivative.⁵ The present procedure is an adaptation of that described by Gösl and Meuwsen.³

4. Merits of the Preparation

This procedure is a convenient and general method for preparing asymmetrically substituted hydrazines.³ This is illustrated by the following examples reported by the submitters³ (% yields in parentheses): methylamine to methylhydrazinium hydrogen sulfate (49–53%); ethylamine to ethylhydrazinium hydrogen oxalate (51%); butylamine to butylhydrazinium hydrogen sulfate (49–56%); piperidine to 1-aminopiperidinium hydrogen oxalate (32%); dibutylamine to 1,1-dibutylhydrazinium hydrogen oxalate (34%); trimethylamine to 1,1,1-trimethylhydrazinium hydrogen oxalate (79–85%); 2-picoline to 1-amino-2-methylpyridinium iodide (57%); 2,4-lutidine to 1-amino-2,4-dimethylpyridinium iodide (40%); 2,6-lutidine to 1-amino-2,6-

dimethylpyridinium iodide (34%); 2,4,6-collidine to 1-amino-2,4,6-trimethylpyridinium iodide (30%); and quinoline to 1-aminoquinolinium iodide (32%).

Primary, secondary, and tertiary amines can be aminated by chloramine also, but pyridine nitrogens have been aminated only by hydroxylamine-O-sulfonic acid.

It has been shown that, on treatment with base, 1-aminopyridinium iodide undergoes 1,3-dipolar addition with ethyl propiolate or dimethyl acetylenedicarboxylate; thus the N-aminoheterocycles may serve as convenient starting materials for the synthesis of a variety of unusual fused heterocycles.⁶

¹ Institut für Anorganische Chemie der Universität Erlangen, Erlangen, Germany.

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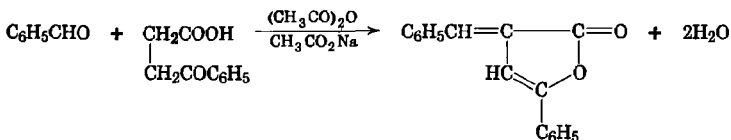
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α -BENZYLIDENE- γ -PHENYL- $\Delta^{\beta,\gamma}$ -BUTENOLIDE

(Cinnamic acid, α -(β -hydroxystyryl)-, γ -lactone)



Submitted by ROBERT FILLER, EDMUND J. PIASEK, and HANS A. LEIPOLD.¹

Checked by S. TROFIMENKO and B. C. MCKUSICK.

1. Procedure

The apparatus consists of a 200-ml., three-necked, round-bottomed flask fitted with thermometer, reflux condenser, and gas-inlet tube. The flask is charged with 17.8 g. (0.10 mole)

of 3-benzoylpropionic acid (Note 1), 10.6 g. (10.6 ml., 0.10 mole) of benzaldehyde, 61.3 g. (57 ml., 0.60 mole) of acetic anhydride, and 8.2 g. (0.10 mole) of powdered anhydrous sodium acetate (freshly fused). The flask is placed in an oil bath maintained at a temperature of 95–100° and is kept there for 2 hours while dry oxygen-free nitrogen is passed through the reaction mixture (Note 2). At the end of this time the flask is removed from the oil bath, and the hot solution is decanted from the sodium acetate into a 250-ml. Erlenmeyer flask. The solution is kept at 0–5° in a refrigerator for 1 hour, during which time α -benzylidene- γ -phenyl- $\Delta^{\delta,\gamma}$ -butenolide separates as an orange solid.

About 40 ml. of 95% ethanol is added to the contents of the flask, and the butenolide is brought into suspension by thoroughly breaking up all lumps with a spatula. The suspension is filtered with suction, and the filter cake is washed with 30 ml. of cold 95% ethanol and then with 100 ml. of boiling water to remove any sodium acetate present. The butenolide is obtained as a yellow solid, m.p. 149–154°, weight 11.1–12.4 g. (45–50%), after being dried overnight in a vacuum desiccator. This product, which is pure enough for most purposes, may be further purified by crystallization from 95% ethanol (Note 3).

2. Notes

1. 3-Benzoylpropionic acid ² is available from Aldrich Chemical Co., Milwaukee, Wisconsin.

2. Oxygen is removed from the nitrogen gas by passing the latter through Brady solution, which consists of zinc amalgam, sodium hydroxide, and sodium anthraquinone- β -sulfonate.³ It has been shown that oxidizing agents induce formation of a Pechmann dye, a deep red substance which is difficult to remove from the butenolide.⁴

3. About 75 ml. of ethanol is used for every gram of butenolide to be dissolved. Clarification of the solution with charcoal should be avoided because the butenolide tends to separate from solution during filtration and clogs the steam-jacketed funnel. The crystallized butenolide melts at 150–152°.

3. Methods of Preparation

α -Benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide has been prepared by the condensation of benzaldehyde with 3-benzoylpropionic acid in the presence of acetic anhydride and sodium acetate.^{5,6}

4. Merits of the Preparation

The method described above may be used for the preparation of a wide variety of butenolides substituted in the arylidene ring with either electron-withdrawing or electron-releasing substituents. γ -Lactones such as α -benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide are isoelectronic with azlactones, but have received much less attention. Like the azlactone ring, the butenolide ring may be opened readily by water, alcohols, or amines to form keto acids, keto esters, or keto amides.⁷ α -Benzylidene- γ -phenyl- $\Delta^{\beta,\gamma}$ -butenolide is smoothly isomerized by aluminum chloride to 4-phenyl-2-naphthoic acid⁸ in 65–75% yield via intramolecular alkylation.

¹ Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois.

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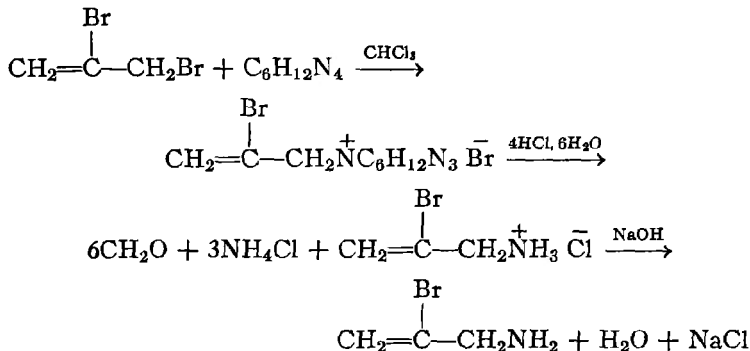
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2-BROMOALLYLAMINE

(Allylamine, 2-bromo-)

Submitted by ALBERT T. BOTTINI, VASU DEV, and JANE KLINCK.¹

Checked by A. S. PAGANO and W. D. EMMONS.

1. Procedure

Caution! Contact with 2-bromoallylamine can cause severe eye and skin irritation. This preparation should be carried out in a good hood, and the operator should wear protective goggles and rubber gloves.

A. *2-Bromoallylhexamminium bromide.* A 2-l. three-necked flask fitted with a Hershberg stirrer,² a dropping funnel, and a condenser is charged with a solution of 154 g. (1.10 moles) of hexamethylenetetramine (Note 1) in 1250 ml. of chloroform. The solution is stirred and heated under reflux while 200 g. (1.00 mole) of 2,3-dibromopropene (Note 2) is added dropwise over a period of 1 hour. Precipitation of the product is noted soon after the first addition of 2,3-dibromopropene. After the addition is complete, the reaction mixture is stirred under reflux for 3 hours and allowed to stand overnight. The mixture is cooled in an ice bath, and the salt is collected by suction filtration. After air-

drying, the crude yellow 2-bromoallylhexaminium bromide weighs 292–308 g. (86–91%) and melts at 183–186°.

B. *2-Bromoallylamine*. Crude 2-bromoallylhexaminium bromide (204 g., 0.60 mole) is dissolved in a warm solution prepared from 400 ml. of water, 2 l. of ethanol, and 480 ml. (5.8 moles) of 12*N* hydrochloric acid. A white precipitate of ammonium chloride forms within an hour. The reaction mixture is allowed to stand for 24 hours, and the precipitate is removed by suction filtration. The mother liquor is concentrated to a volume of 600 ml. (Note 3), and the precipitate (Note 4) is removed by suction filtration. The mother liquor is evaporated to dryness (Note 5), and the residue is dissolved in 300 ml. of water. The solution is cooled in an ice bath and made strongly alkaline (pH 13) with 6*N* sodium hydroxide solution.

The two-phase mixture is placed in a separatory funnel, and the heavy red-brown oil is separated. The aqueous phase is extracted with 100 ml. of ether. The oil and the ether extract are combined, washed with 50 ml. of saturated sodium chloride, and dried over potassium carbonate. The drying agent is removed by filtration, and the filtrate is distilled. Colorless 2-bromoallylamine is collected at 65–68°/100 mm.; weight 49–59 g. (59–72%); n_D^{25} 1.5075–1.5085 (Note 6).

2. Notes

1. The submitters used hexamethylenetetramine obtained from Matheson, Coleman and Bell.

2. The 2,3-dibromopropene was obtained from Columbia Organic Chemicals Co., Columbia, South Carolina, and was redistilled before use. The preparation of 2,3-dibromopropene is described in an earlier volume of this series.³

3. The submitters divided the mother liquor into 6 equal portions and concentrated each to a volume of 100 ml. at a pressure of 25 mm. in a 1-l. round-bottomed flask on a rotary film evaporator. The rotary film evaporator used was obtained from Cenco Scientific Co., Santa Clara, California.

4. The precipitate is ammonium chloride that contains virtually no 2-bromoallylamine hydrochloride.

5. The submitters used a rotary film evaporator to evaporate the mother liquor at a pressure of 25 mm. in a water bath heated to 90°.

6. 2-Bromoallylamine discolors slowly even when stored at 0° in a dark container. The refractometer to be used for determination of the refractive index should be placed in a good hood.

3. Methods of Preparation

2-Bromoallylamine has been prepared by heating N-(2-bromoallyl)-phthalimide with hydrazine in methanol;⁴ by treatment of 2,3-dibromopropylamine hydrochloride with excess alcoholic potassium hydroxide;⁵ by treatment of 1,2,3-tribromopropane with alcoholic ammonia at 100°;⁶ and by the present procedure.⁷

4. Merits of the Preparation

This method gives better yields than other methods of preparation of 2-bromoallylamine, and it is the most convenient method for the preparation of large quantities of the compound. The procedure illustrates a reaction, the so-called Delépine reaction, that has been used for the preparation of many primary aliphatic amines.⁸⁻¹² A number of primary aliphatic amines have been prepared by this method without isolation of the intermediate hexaminium salt.¹¹ Several preparations of aliphatic aldehydes via the hexaminium salt have been described in earlier volumes of this series.¹³

¹ Department of Chemistry, University of California, Davis, California.

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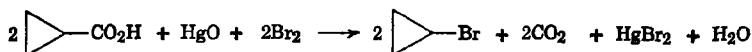
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BROMOCYCLOPROPANE

(Cyclopropane, bromo-)



Submitted by JOHN S. MEEK and DAVID T. OSUGA.¹

Checked by F. S. FAWCETT and B. C. MCKUSICK.

1. Procedure

Twenty-four grams (0.11 mole) of red mercuric oxide (Note 1) and 60 ml. of freshly distilled 1,1,2,2-tetrachloroethane are placed in a 250-ml. three-necked flask equipped with a dropping funnel, a reflux condenser, and a stirrer. A solution of 32.2 g. (0.20 mole) of bromine and 17.2 g. (0.20 mole) of cyclopropanecarboxylic acid in 50 ml. of tetrachloroethane is added dropwise to the stirred suspension of mercuric oxide over a period of 45 minutes, the flask being kept in a water bath at 30–35° (Note 2). The mixture is stirred after the addition of the reactants until the evolution of carbon dioxide ceases.

The flask is then cooled in ice water, and the contents are filtered with as little suction as possible (Note 3). The filter cake is pressed dry and washed with three 15-ml. portions of tetrachloroethane first used to rinse out the flask. The combined filtrates are dried with a little calcium chloride. Sometimes the solution contains a little bromine; it is removed by adding allyl alcohol dropwise until the bromine color is discharged (usually 0.5–1.0 ml. suffices).

The solution is decanted into a 200-ml. round-bottomed flask

containing a carborundum chip. The material is distilled through a 20-cm. column of glass helices or a 30-cm. spinning-band column. The fore-run boiling below $75^{\circ}/760$ mm. is bromocyclopropane pure enough for most purposes; weight 9.8–11.2 g. (41–46%); n_D^{25} 1.455–1.459; d_4^{25} 1.506 (Note 4). Redistillation of this product gives pure bromocyclopropane, b.p. $69^{\circ}/760$ mm., n_D^{25} 1.4570, with but slight loss.

2. Notes

1. The mercuric oxide used was Mallinckrodt or Baker powdered red mercuric oxide, analytical reagent grade. Old mercuric oxide gives variable results and may lower the yield. The 1,1,2,2-tetrachloroethane used was a technical grade and was distilled to make sure no low-boiling impurities were present. Reagent-grade solvent has been used without distillation. The vapors of this chlorinated hydrocarbon are toxic, and its distillation as well as the reaction should be carried out in a hood. Suitable cyclopropanecarboxylic acid ² is obtainable from Aldrich Chemical Company.

2. The reaction starts spontaneously and is mildly exothermic. Moderating the temperature by use of a water bath diminishes the amount of bromine and product carried off by the carbon dioxide evolved. The reaction can be followed by use of a tetrachloroethane bubbler, and at the end of the reaction the solvent in the bubbler can be used to wash the mercuric bromide. The checkers followed the reaction with a wet test meter presaturated with carbon dioxide; 52–60% of the theoretical amount of carbon dioxide was evolved.

3. The checkers used a sintered glass pressure filter (Corning Glass Works, Cat. No. 34020) rather than a suction filter in order to minimize evaporation losses. An ordinary water aspirator can cause the mixture to boil at room temperature. The flask and filter can be cleaned readily with a little acetone, which dissolves mercuric bromide rapidly.

4. Once the boiling point starts to rise, it goes up quite rapidly. The fractions collected between 75° and 90° contain a little product and can be reworked if a second distillation is carried out.

3. Methods of Preparation

Bromocyclopropane has been prepared by the Hunsdiecker reaction by adding silver cyclopropanecarboxylate to bromine in dichlorodifluoromethane at -29° (53% yield) or in tetrachloroethane at -20° to -25° (15–20% yield).³ Decomposition of the peroxide of cyclopropanecarboxylic acid in the presence of carbon tetrabromide gave bromocyclopropane in 43% yield.⁴ An attempt to prepare the bromide via the von Braun reaction was unsuccessful.³

4. Merits of the Preparation

The present procedure is substantially simpler and quicker than the best previous procedure,³ which requires 4 days instead of 4 hours. It is also safer, for no explosions have been encountered with the present procedure, even on a 1.2-mole scale,⁶ whereas care must be taken to prevent explosion of the intermediate hypobromite when the Hunsdiecker method is used,³ and one detonation has been reported.⁶ In comparison with the peroxide method,⁴ it is simpler and gives better yields.

The present procedure seems to be a general one for producing alkyl halides from acids. To aid in isolating higher-boiling or solid products, solvents such as carbon tetrachloride and cyclohexane can be used.⁷ In preparing a solid, the mercuric halide can be removed by extraction with 5% potassium iodide.

¹ Department of Chemistry, University of Colorado, Boulder, Colorado.

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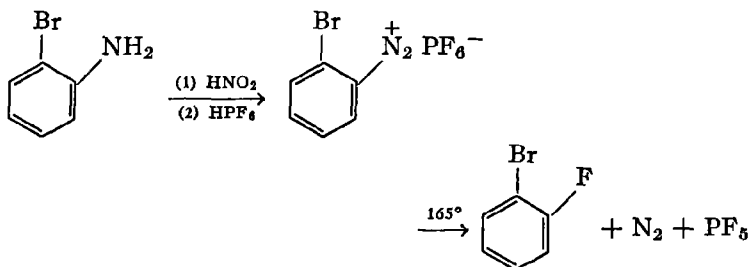
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1-BROMO-2-FLUOROBENZENE

(Benzene, 1-bromo-2-fluoro-)

Submitted by K. G. RUTHERFORD and W. REDMOND.¹

Checked by M. PAULSHOCK and B. C. MCKUSICK.

1. Procedure

A. *o*-Bromobenzenediazonium hexafluorophosphate. A solution of 95 ml. of 12*N* hydrochloric acid in 650 ml. of water is added with stirring to 60 g. of *o*-bromoaniline (0.35 mole; Note 1) in a 2-l. three-necked flask equipped with stirrer and thermometer. Solution is effected by heating the mixture on a steam bath (Note 2). A solution of 29 g. (0.42 mole) of sodium nitrite in 75 ml. of water is added with stirring while the mixture is maintained at -5° to -10° by means of a bath of ice and salt or of dry ice and acetone. At the end of the addition there is an excess of nitrous acid, which can be detected with starch iodide paper. Seventy-four milliliters (134 g., 0.60 mole) of 65% hexafluorophosphoric acid (Note 3) is added in one portion, with vigorous stirring, to the cold solution of the diazonium salt. Cooling and slow stirring are continued for an additional 30 minutes, and the precipitated diazonium hexafluorophosphate is then collected on a Büchner funnel. The diazonium salt is washed on the funnel with 300 ml. of cold water and with a solution of 80 ml. of methanol in 320 ml.

of ether (Note 4). The salt is partly dried by drawing air through the funnel for 2 hours. It is then transferred to a pile of several filter papers, powdered with a spatula, and dried at about 25°/1 mm. for at least 12 hours. The dried *o*-bromobenzenediazonium hexafluorophosphate is cream-colored; weight 108–111 g. (94–97%); m.p. 151–156° (dec.) (Note 5).

B. 1-Bromo-2-fluorobenzene. *Caution! This step should be carried out in a hood because the PF₅ evolved on thermal decomposition of the diazonium salt is poisonous.* The apparatus consists of a 1-l., three-necked, round-bottomed flask equipped with a thermometer, a condenser, a magnetic stirrer (optional), and a 250-ml. Erlenmeyer flask that is attached by means of a short rubber Gooch connecting tube. The dry powdered hexafluorophosphate salt is placed in the Erlenmeyer flask, and 300 ml. of heavy mineral oil is placed in the round-bottomed flask. The mineral oil is heated to 165–170° by means of an oil bath or electric heating mantle and maintained at this temperature while the salt is added rapidly in portions over a period of 30 minutes. The flask is cooled rapidly to room temperature, the side flask is removed, and 400 ml. of 10% aqueous sodium carbonate is added slowly through the condenser. The mixture is steam-distilled until no more oil is visible in the distillate.

The oil, which is heavier than water, is separated, and the aqueous layer is extracted with three 50-ml. portions of methylene chloride. The oil and extracts are combined, dried over anhydrous sodium sulfate, and distilled from a Claisen flask with an indented neck. Colorless 1-bromo-2-fluorobenzene is collected at 58–59°/17 mm. or 156–157°/760 mm.; weight 45–47 g. (73–75% based on *o*-bromoaniline); n_D^{25} 1.5320–1.5325.

2. Notes

1. *o*-Bromoaniline obtained from Eastman Kodak and used without redistillation is satisfactory.

2. The amine is dissolved to ensure its complete conversion to the hydrochloride. The amine hydrochloride may partly crystallize as the solution is cooled, but it redissolves as diazotization proceeds.

3. The 65% hexafluorophosphoric acid (density 1.81) was obtained from the Ozark-Mahoning Company, Tulsa, Oklahoma. A graduated polypropylene (Nalgene®) cylinder was used to contain the measured quantity of the acid. Rubber gloves should be worn as a precautionary measure against burns. Working in a hood prevents any contact of exposed parts of the body with fumes. *In the event of accidental contact of the acid with the skin, the affected place should be immediately washed well with running water and then treated with a paste of magnesium oxide and glycerol² or soaked in ice water.*

4. The methanol-ether filtrate has a slight yellow color. It is not known what impurity is removed by this solvent pair. However, the submitters found that this treatment improved the yield of several aryl fluorides prepared according to the present procedure.

5. The checkers had *o*-bromobenzenediazonium hexafluorophosphate examined in laboratories of the Du Pont Co. Explosives Department to see if it could be detonated. It was found sensitive to neither shock nor static electricity, and to decompose but not detonate when rapidly heated to 250°. Hence it probably does not present an explosion hazard, but it should be kept away from heat, especially if in a closed container.

3. Methods of Preparation

1-Bromo-2-fluorobenzene has been prepared in 37% yield by the Schiemann reaction from *o*-bromoaniline, nitrous acid, and fluoboric acid.^{3,4} The present procedure⁵ is a modification of the Schiemann reaction.

4. Merits of the Preparation

This procedure is a general way of converting arylamines to aryl fluorides, for it has been used to make fifteen other aryl fluorides. It generally gives better yields than the Schiemann reaction.

1-Bromo-2-fluorobenzene is used to prepare the highly reactive intermediate, benzyne.⁶

¹ Department of Chemistry, Essex College, Assumption University of Windsor, Windsor, Ontario, Canada.

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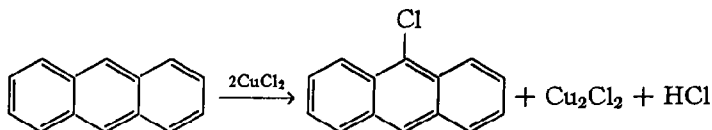
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9-CHLOROANTHRACENE

(Anthracene, 9-chloro-)



Submitted by D. C. NONHEBEL.¹

Checked by R. B. GREENWALD and E. J. COREY.

1. Procedure

In a dry, 1-l., two-necked flask, equipped with a mechanical stirrer and a reflux condenser fitted with a drying tube, are placed 17.8 g. (0.100 mole) of anthracene (Note 1), 27.2 g. (0.202 mole) of anhydrous cupric chloride (Note 2), and 500 ml. of carbon tetrachloride (Note 3). The reaction mixture is stirred and heated under reflux for 18–24 hours. The brown cupric chloride is gradually converted to white cuprous chloride, and hydrogen chloride is gradually evolved. At the end of the reaction the cuprous chloride is removed by filtration, and the carbon tetrachloride solution is passed through a 35-mm. chromatographic column filled with 200 g. of alumina (Note 4). The column is eluted with 400 ml. of carbon tetrachloride. The combined eluates are evaporated to dryness to give 19–21 g. (89–99%) of 9-chloroanthracene as a lemon-yellow solid, m.p. 102–104° (Note 5). Crystallization of the product from petroleum ether

(b.p. 60–80°) gives 16–17 g. (75–80%) of 9-chloroanthracene as yellow needles, m.p. 104–106°.

2. Notes

1. Anthracene, B. D. H. (blue fluorescence), was used. Traces of ethylene glycol, glycerol, ethanol, or water considerably retard the reaction and lead to unsatisfactory results.

2. Anhydrous cupric chloride is dried in an oven at 110–120° for several hours and stored in a desiccator or over phosphorus pentoxide before use.

3. Chlorobenzene or *sym*-tetrachlorethane may be used instead of carbon tetrachloride as solvent, in which case the reaction is complete as soon as the mixture has reached reflux. The product is liable to be contaminated by a small amount of 9,10-dichloroanthracene.

4. Merck alumina or Spence Type H alumina was used.

5. The 9-chloroanthracene at this stage usually contains a small amount of unreacted anthracene.

3. Methods of Preparation

9-Chloroanthracene has been prepared by the action of chlorine,² *tert*-butyl hypochlorite,³ 1,3-dichloro-5,5-dimethylhydantoin,⁴ or phosphorus pentachloride⁵ on anthracene.

4. Merits of the Preparation

The present method is a one-step synthesis giving a high yield of 9-chloroanthracene from readily available starting materials.

It is thought that the chlorination proceeds through a π -complex between cupric chloride and anthracene, and that this complex then undergoes homolytic dissociation.⁶ Hence aromatic rings subject to attack by chlorine atoms can be chlorinated in this way. Thus one can convert pyrene to 1-chloropyrene (90% yield), but phenanthrene is not chlorinated. Analogous procedures using cupric bromide lead to 9-bromoanthracene (99% yield) and 1-bromopyrene (94% yield).⁷

¹ Chemistry Department, Royal College of Science and Technology, Glasgow, Scotland.

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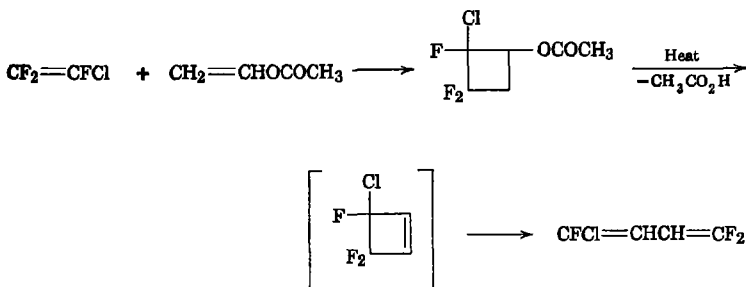
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1-CHLORO-1,4,4-TRIFLUOROBUTADIENE

(Butadiene, 1-chloro-1,4,4-trifluoro-)



Submitted by R. E. PUTNAM, B. C. ANDERSON, and W. H. SHARKEY.¹

Checked by R. D. BIRKENMEYER, M. A. REBENSTORF, and F. KAGAN.²

1. Procedure

A. *2-Chloro-2,3,3-trifluorocyclobutyl acetate* (Note 1). A mixture of 1.0 g. of hydroquinone, 3 drops of a terpene inhibitor (Note 2), and 140 g. (1.63 moles) of inhibited redistilled vinyl acetate (Note 3) is placed in a 400-ml. high-pressure shaker tube lined with stainless steel (Note 4). The shaker tube is closed,

cooled in a mixture of solid carbon dioxide and acetone, evacuated, and charged with 47 g. (0.40 mole) of chlorotrifluoroethylene (Note 5). The shaker tube is heated with agitation to 215° in a period of about 1 hour and is then heated at 215° for 3 hours. The shaker tube is cooled to room temperature and is bled slowly to remove excess chlorotrifluoroethylene. The black, viscous reaction mixture (Note 6) is transferred to a distillation flask and heated on a steam bath. After a fore-run of dichlorohexafluorocyclobutane and vinyl acetate is collected at atmospheric pressure, a receiver cooled in solid carbon dioxide and acetone is attached, and crude 2-chloro-2,3,3-trifluorocyclobutyl acetate is rapidly distilled by gradually reducing the pressure to about 10 mm. (Note 7). Redistillation through a 30-cm. column packed with glass helices provides 22–30 g. (27–37%) (Note 8) of the acetate, b.p. 60–65°/100 mm., n_D^{25} 1.3916–1.3921.

B. *1-Chloro-1,4,4-trifluorobutadiene*. The apparatus is similar to that described in a previous volume.¹² It consists of a "Vycor" glass reaction tube, 60 cm. long by 25 mm. outside diameter, mounted vertically in an electric furnace about 35 cm. long (Note 9). Attached to the top of the tube is a graduated dropping funnel. A thermocouple well extending to the center of the heated section is inserted through the bottom of the tube. The heated section of the tube is packed with quartz tubing (8 mm. outside diameter), cut into 0.5-cm. lengths, and held in place by indentations in the tube. Ten centimeters from the bottom of the tube is a side arm leading successively to two traps cooled with solid carbon dioxide and acetone, an inlet tube for nitrogen, a manometer, and a vacuum pump.

The system is evacuated to a pressure of 5–10 mm., and the tube is heated to 700°, measured at the center of the heated zone. 2-Chloro-2,3,3-trifluorocyclobutyl acetate is admitted at the rate of 10–20 g. per hour. From 70 g. (0.35 mole) of the cyclobutyl acetate there is obtained 62–68 g. of mixed solid and liquid condensate (Note 10). Fractionation through a 30-cm. column packed with glass helices affords 30–35 g. (60–70%) of 1-chloro-1,4,4-trifluorobutadiene (Note 11), b.p. 50–51°, n_D^{25} 1.3870; 18–22 g. of acetic acid; and 7–18 g. of recovered 2-chloro-2,3,3-trifluorocyclobutyl acetate (Note 12).

2. Notes

1. The exact structure of the cyclobutane is not known. Any of the possible isomers would undergo pyrolysis to give 1-chloro-1,4,4-trifluorobutadiene. 2-Chloro-2,3,3-trifluorocyclobutyl acetate is now favored as the structure of the cycloadduct rather than 3-chloro-2,2,3-trifluorocyclobutyl acetate as originally proposed.³ The basis for this preference is mass spectral data. Ions of m/e 64 $[(CF_2=CH_2)^+]$, relative abundance 1.2% and 138 $[(CFCl=CHOCOCH_3)^+]$, relative abundance 0.96% were much more abundant than ions of m/e 80 $[(CFCl=CH_2)^+]$, relative abundance 0.10% and 122 $[(CF_2=CHOCOCH_3)^+]$, relative abundance 0.026%.

2. The purpose of the terpene is to inhibit polymerization of the fluoroolefin. Terpenes that are effective include dipentene and terpinolene.

3. Ordinary commercial-grade vinyl acetate is redistilled. One gram of hydroquinone per 100 g. of vinyl acetate is added to inhibit polymerization of the latter, which is then stored at 0–4° until needed.

4. A shaker tube equipped with a 1200-atm. rupture-disk assembly was used by the submitters. The checkers used a 1270-ml. stainless steel rocking autoclave fitted with a thermocouple well that extended into the reaction mixture and a stainless steel 5000-p.s.i. rupture disk. The agitation rate was 58 cycles per second. Attempts to use a magnetically stirred autoclave were unsuccessful.

5. Chlorotrifluoroethylene is available in 1-lb. and 5-lb. cylinders from the Matheson Company, East Rutherford, New Jersey.

6. The checkers found the reaction mixture to be dark but not viscous. In experiments in which a magnetically stirred autoclave was used, dark viscous reaction mixtures were obtained, but no product.

Difficulties encountered by the checkers when they used a magnetically stirred autoclave led the submitters to re-examine the reaction. It was found that certain batches of vinyl acetate gave very poor yields. In these cases, 27–37% yields were ob-

tained by heating to 175° in 1 hour followed by heating at 175° for 16 hours.

7. The quantity of fore-run depends on the amount of polymerization of vinyl acetate. Distillation of the product through a packed column goes more smoothly, with less heat having to be applied to the distillation flask, if the product has been separated from high-boiling material by a quick preliminary distillation.

8. Up to 25% by weight of the product is ethylidene diacetate. The diacetate can be detected by gas chromatographic analysis using a column of the diglyceride of 6,6,6-trifluorohexanoic acid on firebrick at 120°. ¹⁰ The checkers obtained yields ranging from 24% in a 0.75-scale experiment to 47% on a three-fold increase in scale.

9. A standard tube furnace such as the 120-volt "Multiple Unit" electric furnace manufactured by the Hevi Duty Electric Company was used.

10. Care must be taken to prevent plugging of the first cold trap by solid acetic acid because the back-pressure produced leads to greatly reduced yields and appreciable carbonization. Should plugging occur, the cooling bath is removed and the plug is melted with warm acetone. Some diene will distil into the second trap during this process.

11. 1-Chloro-1,4,4-trifluorobutadiene is a mixture of equal amounts of *cis* and *trans* isomers. This has been demonstrated by gas chromatographic analysis of the mixture on a packed column of high efficiency using Dow-Corning silicone 703 oil or 200 oil on firebrick, or on a capillary gas chromatographic column using squalane as the partitioning liquid.

12. The checkers did not isolate any recovered 2-chloro-2,3,3-trifluorocyclobutyl acetate.

3. Methods of Preparation

The procedure for chlorotrifluorocyclobutyl acetate ³ is a modification of one used by Coffman, Barrick, Cramer, and Raasch ⁴ for the preparation of tetrafluorocyclobutanes from tetrafluoroethylene.

The method for the pyrolysis of chlorotrifluorocyclobutyl

acetate to chlorotrifluorobutadiene is that of Anderson, Putnam, and Sharkey.³

4. Merits of the Preparation

The synthesis of 2-chloro-2,3,3-trifluorocyclobutyl acetate illustrates a general method of preparing cyclobutanes by heating chlorotrifluoroethylene, tetrafluoroethylene, and other highly fluorinated ethylenes with alkenes. The reaction has recently been reviewed.¹¹ Chlorotrifluoroethylene has been shown to form cyclobutanes in this way with acrylonitrile,⁵ vinylidene chloride,⁶ phenylacetylene,⁷ and methyl propiolate.³ A far greater number of cyclobutanes have been prepared from tetrafluoroethylene and alkenes;^{4,11} *when tetrafluoroethylene is used, care must be exercised because of the danger of explosion.* The fluorinated cyclobutanes can be converted to a variety of cyclobutanes, cyclobutenes, and butadienes.

The synthesis of chlorotrifluorobutadiene illustrates a general method that has been used to make tetrafluorobutadiene^{3,8} and substituted fluorodienes.^{3,8,9} The same procedure can be used to transform fluorocyclobutenes and chlorofluorocyclobutenes to the isomeric dienes; 2-methyl-1,1,4,4-tetrafluorobutadiene, 2-chloro-1,1,4,4-tetrafluorobutadiene, and 1-chloro-1,4,4-trifluoro-2-phenylbutadiene have been made thus.³

¹ Contribution No. 597 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

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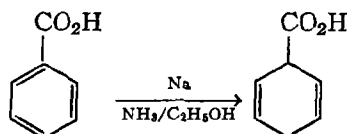
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1,4-DIHYDROBENZOIC ACID**(2,5-Cyclohexadiene-1-carboxylic acid)**Submitted by M. E. KUEHNE and B. F. LAMBERT.¹

Checked by LOUISE KUDA and V. BOEKELHEIDE.

1. Procedure

Ten grams (0.082 mole) of benzoic acid is added to 100 ml. of anhydrous ethanol in a 2-l. three-necked flask equipped with a mechanical stirrer and with loose cotton plugs in the side necks. After the benzoic acid has dissolved, 600 ml. of liquid ammonia (Note 1) is added to the stirred solution. Then 6.2 g. (0.27 g. atom) of sodium is added in small pieces. When about one-third of the sodium has been added, the white sodium salt of the acid precipitates, and there is strong foaming of the reaction mixture. After all the sodium has been consumed, as evidenced by the disappearance of the blue color, 14.6 g. (0.27 mole) of ammonium chloride is added cautiously. The mixture is stirred for an additional hour and then allowed to stand until the ammonia has evaporated.

The residue is dissolved in 300 ml. of water. The solution is poured onto 200 g. of ice and acidified to a pH of about 4 by addition of 75 ml. of 10% hydrochloric acid. The resulting mixture is extracted with four 100-ml. portions of peroxide-free ether, and the combined extracts are washed with 50 ml. of a saturated aqueous solution of sodium chloride and dried over 2 g. of anhydrous magnesium sulfate (Note 2). The ether solution is separated from the drying agent and concentrated at room temperature under reduced pressure. The residual oil is distilled from a 25-ml.

Claisen flask with an indented neck. 1,4-Dihydrobenzoic acid is obtained as a colorless oil; weight 9.0–9.7 g. (89–95%); b.p. 80–98°/0.01 mm.; n_D^{24} 1.5011. This material is sufficiently pure for most purposes. However, by a careful redistillation, a small fore-run (b.p. 80–90°/0.01 mm.; n_D^{24} 1.5000) can be separated, and the remainder of the material (b.p. 91–97°/0.01 mm.; n_D^{24} 1.5019) solidifies on cooling; m.p. 15–17° (Note 3). It is stored under nitrogen in a closed vessel (Note 4).

2. Notes

1. Arrangements for cooling or condensing the ammonia can be made, but are not necessary. Most simply, the liquid ammonia can be passed directly from a cylinder into the reaction vessel through heavy rubber tubing.

2. 1,4-Dihydrobenzoic acid has a very penetrating, repulsive odor, and care should be taken to avoid contamination of hands or clothing.

3. Samples of the 1,4-dihydrobenzoic acid, after both the first and the second distillations, are transparent in the ultraviolet region between 220 m μ and 300 m μ , indicating the absence of benzoic acid or conjugated dihydrobenzoic acids. The refractive index cited in Reference 3 is in error.

4. In the presence of air, 1,4-dihydrobenzoic acid slowly gives benzoic acid and hydrogen peroxide.²

3. Method of Preparation

Apparently, 1,4-dihydrobenzoic acid has been prepared only by the Birch reduction of benzoic acid, as illustrated by the present procedure.^{2,3}

4. Merits of the Preparation

This procedure is illustrative of the general method of reduction of aromatic compounds by alkali metals in liquid ammonia known as the Birch reduction. The theoretical and preparative aspects of the Birch reduction have been discussed in excellent reviews,⁴⁻⁶

and there is another example of a Birch reduction in *Organic Syntheses*.⁷ Of particular interest in the present procedure is the effect of having a group that forms a stable anion with the alkali metal. For both simple aromatic acids and amides, a Birch reduction gives the corresponding 1,4-dihydro derivative. The same is true when *o*-alkyl or *o*-methoxyl groups are present. However, with *p*-alkyl or *m*-methoxyl substituents, the corresponding tetrahydro derivatives are formed. *p*-Methoxyl or *p*-acetamino groups, which can form stable anionic fragments, are lost during such reductions.

The following examples may be cited to illustrate these generalizations. *p*-Toluic acid under conditions of the Birch reduction essentially as given in this procedure yields mainly 1,2,3,4-tetrahydro-*p*-toluic acid (*cis* and *trans*) plus minor amounts of 1,4-dihydro-*p*-toluic acid (*cis* and *trans*).⁸ *o*-Toluic acid gives 1,4-dihydro-*o*-toluic acid in 73% yield;⁸ *m*-methoxybenzoic acid gives 1,4,5,6-tetrahydro-3-methoxybenzoic acid in 32% yield;⁹ *o*-methoxybenzoic acid gives crude 1,4-dihydro-2-methoxybenzoic acid in 80% yield;¹⁰ 3,4,5-trimethoxybenzoic acid gives 1,4-dihydro-3,5-dimethoxybenzoic acid in 87% yield;⁸ 4-acetaminobenzoic acid gives 1,4-dihydrobenzoic acid in 75% yield;⁸ benzamide gives 1,4-dihydrobenzamide in 69% yield;⁸ *m*-methoxybenzamide gives 1,4-dihydro-3-methoxybenzamide in 30% yield;⁸ 3,4,5-trimethoxybenzamide gives 1,4-dihydro-3,5-dimethoxybenzamide in 73% yield;⁸ and 3,5-dimethoxybenzamide gives 1,4-dihydro-3,5-dimethoxybenzamide in 59% yield.⁸ Thus the present example of the Birch reduction illustrates a useful and general synthetic method for preparing dihydro aromatic derivatives.

¹ Ciba Pharmaceutical Products Inc., Summit, New Jersey.

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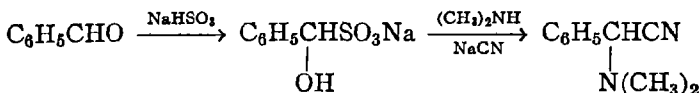
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α -N,N-DIMETHYLAMINOPHENYLACETONITRILE

(Glycinonitrile, N,N-dimethyl-2-phenyl-)

Submitted by HAROLD M. TAYLOR and CHARLES R. HAUSER.¹

Checked by W. BRUCE KOVER and JOHN D. ROBERTS.

1. Procedure

A mixture of 1.5 l. of water and 624 g. (6.00 moles) of sodium bisulfite in a 5-l. beaker equipped with a mechanical stirrer is stirred until solution is complete. Benzaldehyde (Note 1) (636 g., 6.00 moles) is added and the mixture is stirred for 20 minutes, during which time a slurry of the benzaldehyde-bisulfite addition product is formed. A 25% aqueous solution of dimethylamine (1100 g.) containing 275 g. (6.13 moles) of the amine is run in, and stirring is continued as most of the addition compound dissolves. The beaker is immersed in an ice bath, and 294 g. (6.00 moles) of sodium cyanide (*Caution! Toxic*) is added over a period of 20–25 minutes.

The ice bath is removed after addition of the sodium cyanide, and the mixture is stirred for 4 hours. The organic layer is separated, and the aqueous layer is extracted with three 500-ml. portions of ether. The combined ethereal extracts and organic layer are washed with two 100-ml. portions of cold water and dried over anhydrous magnesium sulfate. The ethereal solution is filtered, and the ether is removed at atmospheric pressure. The residue is transferred to a vacuum distillation system and distilled under reduced pressure (*Caution! See Note 2*). The yield of α -dimethylaminophenylacetonitrile boiling at 88–90°/1.9–2.1 mm. is 842–844 g. (87–88%) (Notes 3 and 4).

2. Notes

1. Eastman Kodak benzaldehyde (white label grade) was used without further purification.

2. Occasionally the odor of hydrogen cyanide can be detected during the distillation, even when a trap filled with sodium hydroxide pellets precedes the usual trap cooled in dry ice and acetone to protect the pump. For safety, the vacuum pump should be placed in a hood, or provision should be made for the pump exhaust to be vented into a hood or out-of-doors during the distillation.

3. Anhydrous dimethylamine has been used by the submitters in a slightly different procedure to give yields up to 95% of the theory.

4. The checkers carried out the preparation with one-half of the specified quantities without any decrease in the yield.

3. Methods of Preparation

The procedure described above is a modification of that of Hauser, Taylor, and Ledford ² and of Luten ³ which avoids use of anhydrous dimethylamine. It is related to the procedure of Goodson and Christopher ⁴ that employs benzaldehyde, aqueous dimethylamine hydrochloride, and potassium cyanide.

The product can also be prepared from benzaldehyde, dimethylamine, and potassium cyanide in cold acetic acid and aqueous ethanol.⁵

4. Merits of the Preparation

The method can be used to prepare a number of α -aminonitriles from aliphatic or aromatic aldehydes and ketones and secondary aliphatic amines.⁶

The nitrile group of α -N,N-dimethylphenylacetone nitrile can generally be replaced by an alkyl or aryl group of a Grignard reagent to form the corresponding tertiary amines.^{4,7} The α -hydrogen of the aminonitrile can be alkylated,^{2,7} and the resulting alkylation product can be converted to enamines ² or to ketones.⁷

¹ Department of Chemistry, Duke University, Durham, North Carolina.

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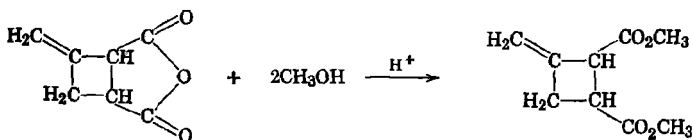
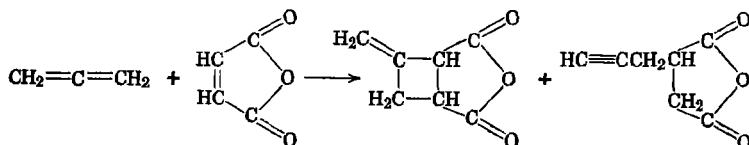
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**DIMETHYL
3-METHYLENECYCLOBUTANE-1,2-DICARBOXYLATE**
(3-Methylenecyclobutane-1,2-dicarboxylic acid, dimethyl ester)



Submitted by H. B. STEVENSON, H. N. CRIPPS, and J. K. WILLIAMS.¹

Checked by R. D. BIRKENMEYER, W. E. RUSSEY, and F. KAGAN.²

1. Procedure

A. 3-Methylenecyclobutane-1,2-dicarboxylic anhydride. A 2-l. stainless steel autoclave equipped with stirrer, pressure gauge, and thermocouple is charged with 500 g. (5.1 moles) of maleic anhydride, 645 ml. of benzene, and 0.25 g. of hydroquinone. The autoclave is closed, cooled to -70° with stirring, and evacuated to a pressure of about 20 mm. Allene³ (100 g., 2.5 moles) (Note 1)

is sucked into the autoclave, and the mixture is heated with stirring for 8–10 hours at 200–210°. During this time, the pressure drops from 23 atm. to 15 atm. The vessel is cooled to 25°, and unreacted allene (6–13 g.) is vented into a cold trap (Note 2). The benzene solution is decanted, and about 500 ml. of acetone is added to the autoclave and stirred until the dark viscous residue goes into solution. The benzene and acetone solutions are combined, filtered, and distilled through a 19-mm. x 1.8-m. Nester spinning-band still.⁴ When the pot temperature reaches 170°, the pressure is reduced to 40 mm., and up to 250 g. of maleic anhydride, b.p. 110–115°/40 mm., is recovered. Finally 119 g. of crude anhydride mixture, b.p. 70–125°/3 mm. (Note 3), is collected.

The crude anhydride is carefully fractionated through a 13-mm. x 1.2-m. Nester still at a pressure of 25 mm. (Note 4) and a reflux ratio of at least 10:1. After a fore-run of maleic anhydride, b.p. 50–100°/25 mm., and a small intermediate fraction, there is obtained 75–90 g. (22–26%) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride; b.p. 155–159°/25 mm.; n_D^{25} 1.4935–1.4952 (Note 5). This material is of sufficient purity for most uses, but it contains approximately 2–5% of propargylsuccinic anhydride. Redistillation through the Nester still gives 65–80 g. (19–23%) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride; b.p. 155°/25 mm.; n_D^{25} 1.4946–1.4955.

By continuing the distillation after removal of the cyclobutane anhydride, there is obtained 25–30 g. (7–9%) of propargylsuccinic anhydride; b.p. 162–168°/25 mm.; m.p. 63–68°. The melting point is raised to 69–70° by one recrystallization from 100 ml. of benzene (80% recovery of purified product).

B. *Dimethyl 3-methylenecyclobutane-1,2-dicarboxylate*. One liter of methanol is added cautiously with occasional shaking to 276 g. (2.00 moles) of 3-methylenecyclobutane-1,2-dicarboxylic anhydride (n_D^{25} 1.4946–1.4955; Note 6) and 5 g. of *p*-toluenesulfonic acid in a 2-l. three-necked flask fitted with a thermometer, a condenser, and a dropping funnel. Refluxing starts after about two-thirds of the methanol has been added. The remainder is added at a rate that maintains vigorous boiling. The solution is refluxed for 30–40 hours with the pot temperature increasing

from 67° to 68° (Note 7). The mixture is cooled to 15°, and methanol and water are removed by distillation under reduced pressure at temperatures below 15°, using a large receiver cooled with a mixture of solid carbon dioxide and acetone. When the pressure goes below 1 mm., the temperature is increased to 50° until the distillation is completed. One liter of methanol (Note 8) is added to the residue, and the solution is heated under reflux for an additional 30–40 hours, during which time the pot temperature increases from 67° to 67.5°. The solution is cooled to 15°, 1.7 g. of finely powdered anhydrous sodium carbonate is added to neutralize the *p*-toluenesulfonic acid, and the methanol and water are removed as before. Crude dimethyl 3-methylene-cyclobutane-1,2-dicarboxylate is distilled rapidly at 65–85°/1 mm. through a 30-cm. Vigreux column (Note 9). The ester can be purified by redistillation through a 13-mm. x 1.2-m. Nester still, with the main fraction boiling at 134–137°/25 mm.; weight 297–338 g. (81–92%); n_D^{25} 1.4624–1.4630.

2. Notes

1. Freshly distilled allene should be used. It should be free of 2-chloropropene, usually present in allene prepared by zinc dehalogenation of 2,3-dichloropropene,³ to avoid formation of chlorine-containing products that liberate hydrogen chloride on distillation.

2. The impurities present in the original allene are concentrated in the recovered material. If recovered allene is to be re-used, it should be fractionated first.

3. The checkers isolated 167 g. of crude anhydride mixture boiling at 70–125°/3 mm. The large tarry residue contains allene polymers and small amounts of 1,2,3,4,5,6,7,8-octahydronaphthalene-2,3,6,7-tetracarboxylic dianhydride, which can be recovered by diluting the residue with benzene and filtering.

4. Pot temperatures above 175°, which result from use of pressures above 25 mm., cause formation of high-boiling by-products.

5. Collection of the product fraction should begin after a few milliliters of an intermediate fraction has been collected at 155°/25 mm. This material has a low index of refraction.

6. The checkers found that the use of anhydride with n_D^{25} 1.4937–1.4945 led to a product with a low index of refraction (n_D^{25} 1.4616).

7. The temperature rises because of disappearance of methanol by conversion to the methyl ester. Attainment of equilibrium is signified by the pot temperature reaching a constant temperature.

8. The second treatment with methanol increases the yield from 60% to 90%.

9. Rapid distillation from the neutralized catalyst results in much smaller loss of ester than is encountered in the more usual procedure that includes washing with water and drying.

3. Methods of Preparation

The procedure used is essentially that described by Cripps, Williams, and Sharkey.⁵ The anhydride has been prepared in a similar manner by Alder and Ackermann.⁶ No other methods have been described for the preparation of these materials.

4. Merits of the Preparation

The first step of this procedure illustrates a general reaction, the addition of allenes to alkenes to form methylenecyclobutanes. The reaction has been reviewed recently.⁷

Since 3-methylenecyclobutane-1,2-dicarboxylic anhydride is easily converted to 3-methyl-2-cyclobutene-1,2-dicarboxylic acid,⁸ it is an intermediate to a variety of cyclobutenes. The dimethyl ester of 3-methylenecyclobutane-1,2-dicarboxylic acid is also a versatile compound; on pyrolysis it gives the substituted allene, methyl butadienoate,⁹ and on treatment with amines it gives a cyclobutene, dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate.⁸

¹ Contribution No. 567 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

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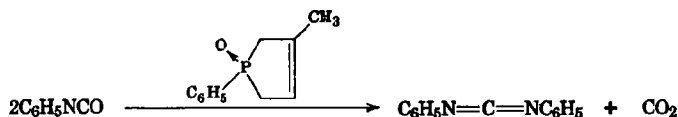
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DIPHENYLCARBODIIMIDE

(Carbodiimide, diphenyl-)



Submitted by T. W. CAMPBELL¹ and J. J. MONAGLE.

Checked by W. S. WADSWORTH and W. D. EMMONS.

1. Procedure

A 250-ml. four-necked flask is fitted with a sealed mechanical stirrer, a condenser protected by a drying tube, a thermometer, and a gas inlet. The flask is swept with a slow stream of nitrogen (Note 1) and dried by flaming. One hundred milliliters (108 g., 0.91 mole) of phenyl isocyanate (Note 2) is pipetted into the flask. One gram (0.052 mole) of 3-methyl-1-phenyl-3-phospholene 1-oxide² is added (Note 3), and the reaction mixture is heated at 50° under nitrogen for 2.5 hours (Note 4); at this point only a faint test for carbon dioxide is obtained when the off-gas is passed through saturated calcium hydroxide solution. The reaction mixture is cooled and rapidly transferred to a Claisen flask. Distillation yields 72–82 g. (82–93%) of diphenylcarbodiimide, obtained as a clear water-white oil, b.p. 110–112°/0.2 mm., n_D^{25} 1.6360–1.6362 (Note 5).

2. Notes

1. Commercial nitrogen is dried by passage through concentrated sulfuric acid.

2. Best results were obtained with material obtained from

Eastman Kodak Company. Either freshly distilled material or material from a freshly opened bottle may be used. Material obtained from several other sources gave variable results even after redistillation.

3. Since the phosphine oxides are very hygroscopic and the reaction rate is sensitive to traces of moisture, the catalyst can be conveniently stored and added to the reaction mixture in long-necked, thin-walled glass ampoules. The catalyst may be dried by distillation (b.p. 168–170°/1.4 mm.) into a receiver containing the inverted ampoules. When sufficient catalyst has distilled to fill the ampoules, nitrogen is bled into the receiver, forcing the catalyst into the ampoules. An ampoule about 15 mm. in diameter will hold about 1 g. of catalyst. A small air space should be left to facilitate crushing the ampoule.

4. Use of more catalyst or higher temperature leads to an increasingly vigorous evolution of carbon dioxide.

5. Diphenylcarbodiimide can be stored for several weeks at 0°. At room temperature it gradually solidifies to a mixture of trimer and polymer. The monomer can be separated from the solid by vacuum distillation.

3. Methods of Preparation

Carbodiimides have been prepared by desulfurization of thio-ureas by metal oxides,³ by sodium hypochlorite,⁴ or by ethyl chloroformate in the presence of a tertiary amine;⁵ by halogenation of ureas or thioureas followed by dehydrohalogenation of the *N,N'*-disubstituted carbamic chloride;⁶ and by dehydration of disubstituted ureas using *p*-toluenesulfonyl chloride and pyridine.⁷ The method described above is a modification of that of Campbell and Verbanc.⁸

4. Merits of the Preparation

This method may be applied to the synthesis of a variety of aryl and alkyl carbodiimides.⁹ Other catalysts may also be used,¹⁰ but the especially active one described here is the one most easily obtained. The method is superior to other methods

reported in that it provides pure products under very simple and mild conditions, allows the use of readily available isocyanates with or without the use of solvent, and offers extremely easy work-up.

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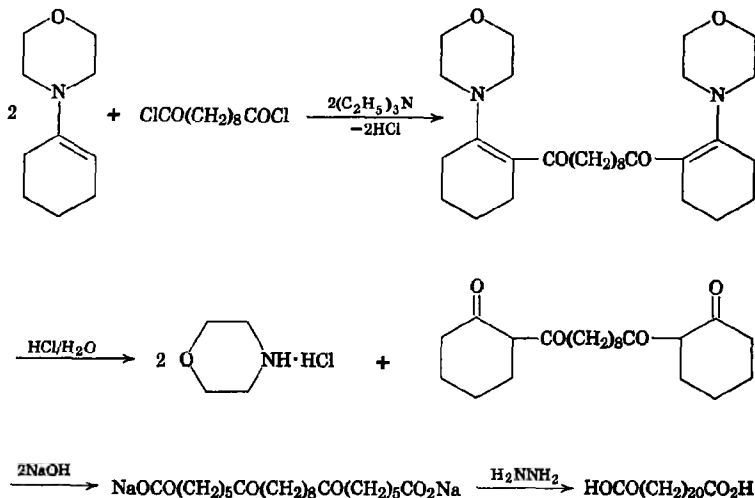
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DOCOSANEDIOIC ACID

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1. Procedure

A. *2,2'-Sebacoyldicyclohexanone*. A solution of 167 g. (1.00 mole) of 1-morpholino-1-cyclohexene² and 101 g. (139 ml., 1.00 mole) of anhydrous triethylamine in 500 ml. of dry chloroform (Note 1) is put in a 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser. Tubes of calcium chloride are inserted in the open ends of the dropping funnel and reflux condenser. The reaction flask is immersed in a water bath at 35°, and a solution of 120 g. (0.50 mole) of sebacoyl chloride (Note 2) in 200 ml. of dry chloroform is added to the well-stirred reaction mixture over a period of about 1.5 hours. The reaction mixture gradually as-

sumes an orange to red color, and a solid precipitates. The reaction mixture is stirred for an additional 3 hours at 35°, 500 ml. of 20% hydrochloric acid is added, and the mixture is boiled under reflux for 5 hours with vigorous stirring. The reaction mixture is cooled to room temperature, and the chloroform layer is separated and extracted with six 150-ml. portions of water. The washings and the aqueous phase are combined, adjusted to a pH of 5-6 with 25% sodium hydroxide solution, and extracted with five 100-ml. portions of chloroform. The chloroform extracts are combined with the chloroform layer, and the chloroform is removed by distillation on a steam bath. The residue gradually congeals to an oily solid on standing at room temperature under a pressure of 10-50 mm. The yield of crude 2,2'-sebacyldicyclohexanone is 181-192 g. (100-106%) (Note 3).

B. Disodium 7,16-diketodocosanedioate. A mixture of 120 g. (3.00 moles) of sodium hydroxide and 1.4 l. of commercial absolute ethanol is refluxed with mechanical stirring in a 5-l. round-bottomed flask until all the sodium hydroxide is dissolved (about 2 hours). The solution is cooled to room temperature, and a warm solution of the crude 2,2'-sebacyldicyclohexanone from Step A in 300 ml. of absolute ethanol is added. The mixture is brought to a boil on a water bath or steam bath in the course of about 15 minutes and is then refluxed for 1 hour. Colorless disodium 7,16-diketodocosanedioate separates during the heating. The reaction mixture, now a thick mush, is cooled to room temperature, and the salt is collected on a 25-cm. Büchner funnel and pressed as dry as possible, preferably with the aid of a rubber dam. The moist salt is suspended in 1 l. of absolute ethanol with mechanical stirring and is then collected on the Büchner funnel as before. After being dried in air, the crude colorless disodium 7,16-diketodocosanedioate weighs 248-255 g. (112-115%, based on 1-morpholino-1-cyclohexene). It is pure enough for the following reduction to docosanedioic acid (Note 4).

C. Docosanedioic acid. All the crude disodium 7,16-diketodocosanedioate of Step B is added to 1 l. of triethanolamine in a 5-l. round-bottomed flask equipped with a reflux condenser, a thermometer, a mechanical stirrer, and a deep oil bath. The mixture is heated under reflux until all the salt dissolves (about 15 min-

utes). The solution is cooled to 130°, 610 ml. (10 moles) of 82% hydrazine hydrate is added through the reflux condenser, and the mixture is refluxed for 4 hours (Note 5).

Potassium hydroxide (168 g., 3.0 moles) is dissolved in 400 ml. of triethanolamine by heating the mixture to boiling in a 1-l. Erlenmeyer flask (about 15 minutes is required). At the end of the reflux period, the hot reaction mixture is transferred to a good hood if it is not already in one, the condenser is removed, and the hot potassium hydroxide solution is added cautiously but rapidly to the stirred reaction mixture (Note 6). The open reaction mixture is at least two-thirds immersed in the oil bath to help prevent foaming over and is heated strongly and rapidly in order to drive off water and excess hydrazine hydrate. After 2-3 hours the temperature inside the flask reaches about 140°, and decomposition of the bis-hydrazone begins, with evolution of nitrogen and considerable foaming. Foaming over is prevented by judicious regulation of the heating, good stirring, and occasional addition of a little silicone oil, which is a good antifoaming agent (Note 7). The temperature is raised as rapidly as possible to 195° (about 2 hours is needed) and held at this temperature for 6 hours. The final oil bath temperature is 200-220°.

The reaction mixture is cooled to about 100° (Note 5), washed out of the flask with 5 l. of hot water (Note 8), and acidified to a pH between 2 and 3 with 1.4 l. of 12*N* hydrochloric acid. The mixture is cooled to room temperature, and the docosanedioic acid that has precipitated is collected on a 25-cm. Büchner funnel and pressed as dry as possible (Note 9). The filter cake is suspended in 5 l. of water with mechanical stirring and collected on the Büchner funnel as before. The moist filter cake is dissolved in 700 ml. of hot 2-methoxyethanol, the hot solution is filtered through a fluted paper in a heated funnel, and the filtrate is gradually cooled to 0-5°. The docosanedioic acid that crystallizes out is separated on a Büchner funnel, pressed as dry as possible, and suspended in 500 ml. of 95% ethanol with mechanical stirring. The acid is collected on a Büchner funnel, washed with a little 95% ethanol, dried in air, and pulverized. The colorless docosanedioic acid thus obtained weighs 127-133 g. (69-72%, based on 1-morpholino-1-cyclohexene) and is nearly

pure; m.p. 124–126°; neutralization equivalent 181–184 (calculated, 185) (Notes 10 and 11).

2. Notes

1. Satisfactory chloroform is obtained by washing 2 l. of commercial chloroform with two 100-ml. portions of 2*N* sodium carbonate solution and two 200-ml. portions of water and distilling it until no more water codistills and the boiling point is 61°. The material remaining in the distillation pot is used without distillation.

2. Satisfactory sebacyl chloride can be purchased from the Eastman Kodak Co., Rochester, New York. The submitters prepared it as follows. A mixture of 150 g. (0.74 mole) of sebacic acid and 150 ml. of thionyl chloride is heated in a water bath at 60°. The acid gradually goes into solution with evolution of sulfur dioxide and hydrogen chloride. When gas evolution ceases, the mixture is distilled as rapidly as possible under reduced pressure. The yield of sebacyl chloride, b.p. 171–175°/15 mm., is about 140 g. (79%). *Caution! Toward the end of the distillation, spontaneous decomposition of the residue with formation of a voluminous black foam frequently occurs.*

3. The tetraketone can be obtained in a pure form by recrystallizing it first from ether with the addition of decolorizing carbon and then from *n*-butanol; yield 50–58%; m.p. 68–72°.

4. The submitters obtained pure 7,16-diketodocosanedioic acid by the following procedure. A solution of 300 ml. of 12*N* hydrochloric acid in 3 l. of water is stirred into a warm solution of 250 g. of the crude disodium 7,16-diketodocosanedioate in 3 l. of water. The resultant suspension of the diketo acid is boiled for a few minutes to make the acid easier to filter, then cooled to room temperature and collected on a Büchner funnel. The filter cake is suspended in 3 l. of water with mechanical stirring and collected on a Büchner funnel, and this procedure is repeated. The moist well-pressed filter cake is recrystallized from 600 ml. of 2-methoxyethanol. The recrystallized acid is suspended in 500 ml. of 95% ethanol, separated on a Büchner funnel, and dried in air. About 120 g. (61%) of pure 7,16-diketodocosanedioic acid is ob-

tained; m.p. 127–129°; equivalent weight 196 ($-\text{CO}_2\text{H}$), 200 ($>\text{C}=\text{O}$) (calculated, 199).

5. One may interrupt the procedure at this point and allow the mixture to stand overnight at room temperature.

6. It is essential for good results that the procedure not be interrupted from the time that the potassium hydroxide solution is added until the time that the 6-hour heating at 195° is completed.

7. Additional security against foaming over is provided by a glass tube that projects into the neck of the flask and is attached to a water pump. The checkers found it helpful to use a Hershberg stirrer with two wire blades; the upper blade was adjusted so that its ends extended above the surface of the reaction mixture and into the foam.

8. The aqueous mixture is not clear because the sodium salt is sparingly soluble in water.

9. The precipitate can be more rapidly separated by means of a centrifuge.

10. Very pure docosanedioic acid can be obtained by another recrystallization from about 450 ml. of 2-methoxyethanol. The recrystallized acid is collected on a Büchner funnel, and the well-pressed filter cake is suspended in 200 ml. of 95% ethanol, re-filtered, and dried in air; weight 112 g. (61%); m.p. 126–127°; neutralization equivalent, 185–187.

11. The checkers found it slightly more convenient to recrystallize the moist crude docosanedioic acid from 1 l. of methyl ethyl ketone. The hot solution is filtered and cooled, and the acid is collected on a Büchner funnel, washed with methyl ethyl ketone, and dried in air.

3. Methods of Preparation

Docosanedioic acid has been prepared by Wolff-Kishner reduction of 6,17-diketodocosanedioic acid, formed by reaction of the half-ester acid chloride of adipic acid with the α,ω -cadmium derivative of decane (%26 overall yield).³ Reduction of ω -[5-(ω -carboxy-*n*-octyl)-2-thenoyl]caprylic acid by the Wolff-Kishner method, followed by simultaneous reduction and desulfurization with Raney nickel of the 2,5-bis(ω -carboxyooctyl)thiophene pro-

duced, is reported to yield docosanedioic acid in 68% overall yield.⁴ Other routes to docosanedioic acid include electrolysis of the monomethyl ester of dodecanedioic acid (43% yield);⁵ oxidative coupling of 10-undecynoic acid to docosa-10,12-diyne-dioic acid (90% yield) and reduction of this intermediate with a palladium catalyst;⁶ and reaction of α,ω -diiodoeicosane with potassium cyanide followed by hydrolysis of the dinitrile produced.⁷

The present method of making docosanedioic acid has been described by Hünig and Lücke.⁸ The Wolff-Kishner reduction of the diketonic intermediate is an application of the modification of Gardner, Rand, and Haynes.⁹

4. Merits of the Preparation

The present procedure has been used to convert suberoyl chloride to eicosanedioic acid (44%), and it is probably a general method for increasing by twelve carbon atoms the chain length of dicarboxylic acids whose chain length is eight or more carbon atoms.⁶ A variant of the method, in the first step of which the ester chloride of a dicarboxylic acid is condensed with 1-morpholino-1-cyclohexene, has also been used to prepare dicarboxylic acids. Thus the mono-ester acid chloride of succinic acid has been converted to sebacic acid (48%), that of suberic acid to tetradecanedioic acid (34%), and that of sebacic acid to hexadecanedioic acid (32%).⁸ A general method of increasing the chain length of a carboxylic acid by six carbon atoms is to employ a monoacyl chloride in the present procedure; overall yields of acids from nonanoic to tetracosanoic are 42–48%.¹⁰ 1-Morpholino-1-cyclopentene¹¹ can be used in the same sort of syntheses as 1-morpholino-1-cyclohexene; thus, by starting with it and lauroyl chloride, heptadecanoic acid can be obtained in 60% yield.¹² Similarly, an enamine of cyclododecanone has been used to lengthen the chain of monocarboxylic acids by twelve carbon atoms, and of dicarboxylic acids by twenty-four; for instance, stearic acid has been converted to triacontanoic acid (70%), and suberic acid to pentatricontanedioic acid (40%).¹³

How to decide whether the enamine method or some other

method is better for preparing a given mono- or dicarboxylic acid is discussed in two papers.^{8,10}

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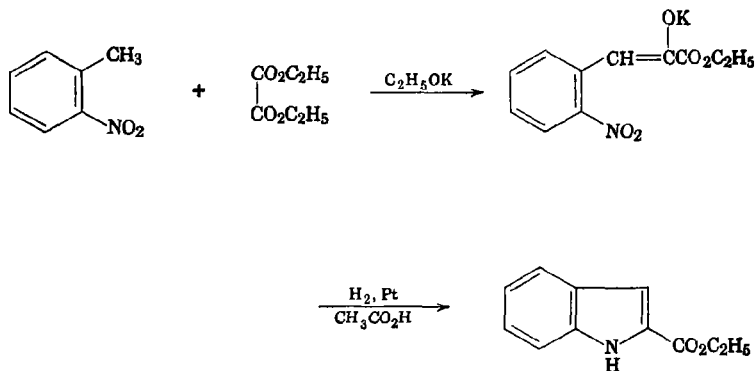
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ETHYL INDOLE-2-CARBOXYLATE

(Indole-2-carboxylic acid, ethyl ester)



Submitted by WAYLAND E. NOLAND and FREDERIC J. BAUDE.¹

Checked by E. J. COREY and RONALD J. McCAULY.

1. Procedure

A. *Potassium salt of ethyl o-nitrophenylpyruvate.* Anhydrous ether (300 ml.) is placed in a 5-l., three-necked, round-bottomed

flask fitted with a 500-ml. dropping funnel, a motor-driven stirrer (with seal), and a reflux condenser protected with a calcium chloride tube. Freshly cut potassium (39.1 g., 1.00 g. atom) is added. *Caution! Follow the precautions for handling potassium described in an earlier volume.*²

A slow stream of dry nitrogen is passed through the flask above the surface of the stirred liquid, and a mixture of 250 ml. of commercial absolute ethanol and 200 ml. of anhydrous ether is added from the dropping funnel just fast enough to maintain mild boiling. When all the potassium has dissolved (Note 1), the nitrogen is shut off. The solution is allowed to cool to room temperature, and 2.5 l. of anhydrous ether is added. Diethyl oxalate (146 g., 1.00 mole) is added with stirring, followed after 10 minutes by 137 g. (1.00 mole) of *o*-nitrotoluene. Stirring is discontinued after an additional 10 minutes, and the mixture is poured, with the aid of a connecting tube, into a 5-l. Erlenmeyer flask. The flask is stoppered and set aside for at least 24 hours. The lumpy deep-purple potassium salt of ethyl *o*-nitrophenylpyruvate is separated by filtration (Note 2) and washed with anhydrous ether until the filtrate remains colorless. The yield of the air-dried salt is 204–215 g. (74–78%).

B. Ethyl indole-2-carboxylate. Thirty grams (0.109 mole) of the potassium salt is placed in a 400-ml. hydrogenation bottle and dissolved by addition of 200 ml. of glacial acetic acid, producing a yellow, opaque solution (Note 3). Platinum catalyst³ (0.20 g.) is added, the bottle is placed in a Parr low-pressure hydrogenation apparatus, and the system is flushed several times with hydrogen. With the initial reading on the pressure gauge about 30 p.s.i., the bottle is shaken until hydrogen uptake ceases and then for an additional 1–2 hours (Note 4). The catalyst is removed by filtration and washed with glacial acetic acid. The filtrate is placed in a 4-l. beaker, and 3 l. of water is added slowly with stirring. Ethyl indole-2-carboxylate precipitates as a yellow solid. It is separated by filtration, washed with five 100-ml. portions of water, and dried over calcium chloride in a desiccator. It weighs 13.2–13.6 g. (64–66%; 47–51% based on *o*-nitrotoluene); m.p. 118–124°.

The dried ester can be further purified by treatment with charcoal and recrystallization from a mixture of methylene chloride and light petroleum ether (b.p. 60–68°). This gives 11.3–11.7 g. (41–44% based on *o*-nitrotoluene) of ethyl indole-2-carboxylate in the form of white needles, m.p. 122.5–124° (Note 5).

2. Notes

1. Complete solution of the potassium takes 1.5–2 hours with stirring and 2.5–3 hours without stirring.

2. Salt that sticks to the sides of the Erlenmeyer flask may be loosened with a piece of 10-mm. glass tubing that has not been fire-polished.

3. On addition of the acetic acid, a small amount of black solid settles out, but this dissolves when the solution is swirled for several minutes. The potassium salt of ethyl *o*-nitrophenylpyruvate, although it undergoes no apparent change in color, does not keep indefinitely in the dry state. After 3 weeks of storage at room temperature, the salt still produced a yellow solution when dissolved in acetic acid, but, after 3 months of storage, the dry salt produced a deep-red solution from which an oil, rather than crystalline ester, was obtained after catalytic hydrogenation.

4. The hydrogen pressure-drop corresponds to 0.325–0.335 mole (99–102%). When the hydrogen pressure drops below about 15 p.s.i., the hydrogen should be replenished in the reservoir tank to bring the pressure back up to about 30 p.s.i. The checkers found a reduction period of 4–6 hours sufficient; the submitters routinely used a 24-hour reduction period.

5. The reported melting points^{4, 6–13} range from 119°⁶ to 125–126°.^{7, 8}

3. Methods of Preparation

The potassium salt of ethyl *o*-nitrophenylpyruvate is prepared essentially according to the method of Wislicenus and Thoma.¹⁴ However, the isolation of ethyl *o*-nitrophenylpyruvate has been eliminated by liberating the ester from its potassium salt in the acetic acid used as solvent for the hydrogenation. Catalytic

hydrogenation of the ester is carried out essentially by the procedure of Brehm.⁵

Ethyl *o*-nitrophenylpyruvate^{4,14} and *o*-nitrophenylpyruvic acid¹⁴⁻²¹ have been prepared by condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium ethoxide,^{4,14} sodium ethoxide,¹⁵⁻²⁰ or sodium methoxide.²¹ Sodium ethoxide is less reactive, however, and cannot be substituted successfully for potassium ethoxide in the present procedure, as it gives a very poor yield and poor quality of precipitated sodium salt. With sodium ethoxide the reaction does not appear to go to completion even under the conditions of refluxing ethanol usually employed,¹⁵⁻²¹ which are considerably more severe than the room temperature conditions employed with potassium ethoxide in the present procedure. *o*-Nitrophenylpyruvic acid has also been prepared by hydrochloric acid hydrolysis of *o*-nitro- α -acetaminocinnamic azlactone.⁴

Ethyl indole-2-carboxylate^{5,13} and the corresponding carboxylic acid^{4,17,18,22,23} have been prepared by reductive cyclization of ethyl *o*-nitrophenylpyruvate and *o*-nitrophenylpyruvic acid, both in the presence of reducing agents such as zinc and acetic acid,^{4,13} ferrous sulfate and ammonium hydroxide,^{17,18,23} and sodium hydrosulfite,^{17,22} and by platinum-catalyzed hydrogenation.⁵ The ethyl ester has also been prepared by esterification^{9,19} of the acid in the presence of sulfuric⁶ and hydrochloric¹² acid catalysts, by the Fischer indole synthesis from ethyl pyruvate phenylhydrazones catalyzed by polyphosphoric acid,¹¹ sulfuric acid and acetic acid,^{11,17} or zinc chloride,²⁴⁻²⁶ and by stannous chloride reduction of ethyl 1-hydroxyindole-2-carboxylate.⁷ Indole-2-carboxylic acid has also been prepared by the Fischer indole synthesis from pyruvic acid phenylhydrazones catalyzed by zinc chloride,²⁴ by the Madelung synthesis from potassium oxalyl-*o*-toluidine,²⁷ by zinc and acetic acid reduction of 1-hydroxy- and 1-methoxyindole-2-carboxylic acids,²⁸ by cyclizative demethanolation of *o*-amino- α -methoxycinnamic acid,²⁹ by reductive cyclization and hydrolysis of *o*-nitrobenzalrhodanine,¹² by alkaline hydrolysis and decarboxylation of dimethyl indole-2,3-dicarboxylate,³⁰ and by fusion of 2-methylindole with potassium hydroxide in the presence of air.³¹

4. Merits of the Preparation

The procedure employs the least expensive commercially available starting materials and requires the minimum number of reaction steps.

Alkaline hydrolysis of ethyl indole-2-carboxylate yields indole-2-carboxylic acid,^{4, 5, 7, 11, 24, 25} which can be decarboxylated to indole by heating at 230°. The acid or its ester serves as a readily accessible indole capable of electrophilic substitution at the 3-position,^{6, 22} and as a precursor for the synthesis of indole-2-acylamino derivatives of interest as model compounds in the study of alkaloid synthesis^{5, 23, 32} and as a degradation product of the mold metabolite, gliotoxin.^{4, 33-35} Reduction of the ester with lithium aluminum hydride yields indole-2-methanol,⁵ which can be oxidized to indole-2-carboxaldehyde by potassium permanganate in acetone.¹⁰ Reduction of the acid chloride with lithium aluminum tri-*tert*-butoxy hydride³⁰ is a convenient synthesis of indole-2-carboxaldehyde.³⁷

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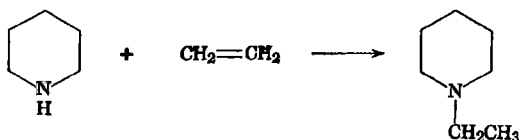
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N-ETHYLPYPERIDINE

(Piperidine, 1-ethyl-)

Submitted by J. WOLLENSAK and R. D. CLOSSON.¹

Checked by C. D. VER NOOY and B. C. MCKUSICK.

1. Procedure

A 1-l. three-necked flask equipped with a reflux condenser, an inlet for dry nitrogen, and a mechanical stirrer is flushed with dry nitrogen. It is then charged with 340 g. (4.00 moles) of piperidine (Note 1), 4.4 g. (0.19 g.-atom) of sodium, and 5.0 g. (5.1 ml., 0.063 mole) of pyridine (Note 2). While a slow stream of nitrogen continues to pass through the flask, the solution is heated under reflux with high-speed stirring for approximately 10 minutes.

During this time most of the sodium reacts without evolution of hydrogen, and the dispersion darkens. The dispersion, which contains some finely divided solids, is cooled and transferred to a 2-l. stirred autoclave (Note 3) under nitrogen. An additional 85 g. (1.00 mole) of piperidine is used to wash the last portions of the dispersion into the autoclave.

The autoclave is pressured with ethylene (Note 2) to 400 lb./in.² with stirring (Note 4). It is then heated to 100° with stirring, which causes the pressure to rise to about 555 lb./in.². It is maintained at 100° with stirring until a gradual drop in pressure ceases; this usually takes about 2.5 hours, but it may take as long as 10 hours (Note 5). The autoclave is cooled to room temperature, and the excess ethylene is vented. The reaction mixture is transferred to a 1-l. round-bottomed flask, the autoclave is rinsed with 100 ml. of methanol that is added to the flask, and the mixture is fractionated through a 90-cm. column packed with glass helices. After a fore-cut of 50–100 g. distilling at 55–129°, 434–468 g. (77–83%) of N-ethylpiperidine is collected; b.p. 129–130.5°; n_D^{20} 1.443–1.444 (Note 6).

2. Notes

1. Piperidine obtained from Eastman Kodak was fractionated through a 90-cm. column packed with glass helices, and the fraction distilling at 105° was used for this work. This material contained approximately 0.36 wt. % of pyridine as indicated by vapor phase chromatography and ultraviolet analysis.

2. Sodium from Ethyl Corporation, pyridine from Eastman Kodak, and c.p. ethylene from Matheson are suitable.

3. The kind of stirrer is not important. The submitters obtained similar results with a three-blade propeller turning at 600 r.p.m. and a paddle stirrer turning at 78 r.p.m. They believe that a rocking autoclave could be substituted for a stirred one.

4. Over half the ethylene pressured into the autoclave dissolves in the piperidine. It is essential to agitate the piperidine during the pressuring operation so that the piperidine will become saturated with ethylene, for otherwise there will not be enough ethylene for the reaction.

5. The checkers found that it shortened the reaction time appreciably to repressure the autoclave to 400–500 lb./in.² whenever the pressure dropped below 350 lb./in.²

6. The checkers got the same results using half the quantities of reactants in a 1-l. stirred autoclave.

3. Methods of Preparation

The described procedure is essentially the method of Closson, Kolka, and Ligett.² Since N-ethylpyperidine was first prepared by Cahours by reaction of piperidine with ethyl iodide,¹ a large number of synthetic methods have been used for its preparation. Reductive alkylation of pyridine with ethanol over Langenback or Raney nickel catalyst gives N-ethylpyperidine in high yield.⁴ The compound may similarly be prepared by catalytic hydrogenation of N-ethylpyridinium chloride with platinum oxide as catalyst⁵ and by the alkylation of piperidine using ethanol and Raney nickel catalyst under hydrogenating conditions.⁶ Other methods that have been used are electrolytic reduction of N-ethylglutarimide,⁷ interaction of pentamethylene oxide and ethylamine at high temperature over aluminum oxide,⁸ interaction of ethylamine and 1,5-dibromopentane,⁹ and reduction of 1-acetylpyperidine with lithium aluminum hydride.¹⁰

4. Merits of the Preparation

The procedure is illustrative of a general method of ethylating amines, wherein one reacts the amine with ethylene using an alkali-metal salt of the amine as catalyst.² Di-*n*-butylamine and *n*-hexylamine have been thus ethylated at 130–160°, aniline, *o*-toluidine, and N-methylaniline at 240–275°. In general, higher olefins add to amines only sluggishly.²

¹ Ethyl Corporation Research Laboratories, Detroit, Michigan.

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GUANIDINE NITRATE

WARNING

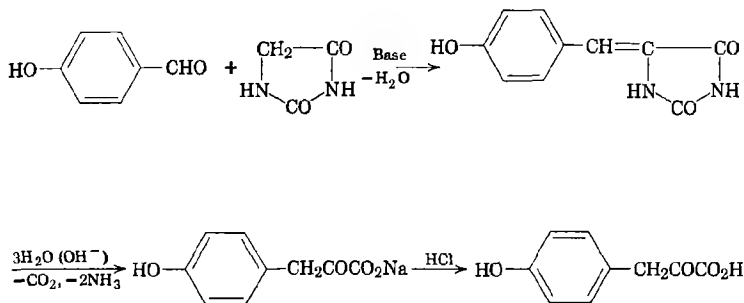
It is strongly recommended that our procedure ¹ not be used to prepare guanidine nitrate. Mixtures of ammonium nitrate and organic materials not much different from the mixture in the procedure are now used extensively as commercial explosives. The aqueous mixture of Note 10 ¹ is similar to some aqueous mixtures used in sizable quantities for rock blasting; a confined mixture of this sort is especially hazardous. Only a few laboratories devoted to explosives research have the barricades and remote control devices needed to run this preparation of guanidine nitrate without risk.

Guanidine nitrate can be bought from Eastman Organic Chemicals and other suppliers.

¹ *Org. Syntheses*, Coll. Vol. **1**, 302 (1941).

***p*-HYDROXYPHENYLPYRUVIC ACID**

[Pyruvic acid, *p*-hydroxyphenyl-]

Submitted by GERHARD BILLEK.¹

Checked by MAX TISHLER and ARTHUR J. ZAMBITO.

1. Procedure

A. 5-(*p*-Hydroxybenzal)hydantoin. An intimate mixture of 6.11 g. (0.050 mole) of *p*-hydroxybenzaldehyde (Note 1) and 5.5 g. (0.055 mole) of hydantoin (Note 2) is placed in a 250-ml. round-bottomed flask. Dry piperidine (10 ml.) is added, a reflux condenser protected by a calcium chloride tube is fitted to the flask, and the flask is immersed in an oil bath so that the level of the reaction mixture is the same as the oil level of the bath. The oil bath is heated slowly to 130° and is held at this temperature for 30 minutes; foaming and gentle boiling occur. The reaction mixture is cooled, and 200 ml. of water at about 60° is added. The contents of the flask are stirred by means of a glass rod until a clear red solution is obtained (Note 3). Any traces of tarry material are removed by filtration. The solution is cooled to room temperature, transferred to an Erlenmeyer flask, and acidified by dropwise addition of 20 ml. of 12*N* hydrochloric acid. The mixture stands at room temperature a few hours, and then the yellow

precipitate of 5-(*p*-hydroxybenzal)hydantoin is collected on a Büchner funnel and washed thoroughly with cold water (Note 4). After being dried in a vacuum desiccator over potassium hydroxide, the crude hydantoin weighs 8.5–8.8 g. (83–86%). It melts at 310–315° (dec.) and is sufficiently pure for the next step and other preparative purposes (Note 5).

B. *p*-Hydroxyphenylpyruvic acid. Crude 5-(*p*-hydroxybenzal)hydantoin (8.5 g., 0.042 mole) and a few chips of porous plate are placed in a 500-ml., three-necked, round-bottomed flask fitted with a reflux condenser, a dropping funnel, and a gas-inlet tube (Note 6). A slow stream of oxygen-free nitrogen (Note 7) is introduced. As soon as the air has been swept out of the apparatus, 240 ml. of 20% aqueous sodium hydroxide solution (w/v) is added through the dropping funnel. The mixture is boiled for 3 hours in an oil bath at 170–180° (Note 8). The 5-(*p*-hydroxybenzal)hydantoin dissolves rapidly, and a clear orange solution is obtained that becomes less deeply colored during the reaction. The reaction mixture is cooled by replacing the oil bath by a bath of cold water. Without interrupting the stream of nitrogen, 100 ml. of 12*N* hydrochloric acid is added through the dropping funnel at such a rate that foaming and heating of the mixture are not excessive. The flask is disconnected, and 5 g. of sodium bicarbonate is dissolved in the mixture (Note 9).

The liquid is transferred to a continuous extractor (Note 10) and extracted with ether until the supernatant layer of ether remains colorless (about 2 hours). The ethereal extract is discarded (Note 11). The aqueous solution is transferred to a 1-l. beaker and acidified by the cautious addition of 60 ml. of 12*N* hydrochloric acid (Note 12). The solution is returned to the extractor, which is attached to a tared round-bottomed flask. The solution is extracted with ether until no more *p*-hydroxyphenylpyruvic acid is obtained (Note 13). The undried ether solution is evaporated to dryness on a boiling water bath to give crude *p*-hydroxyphenylpyruvic acid as a pale-yellow crystalline mass. The mass is broken up with a spatula, and the flask is kept over potassium hydroxide in a vacuum desiccator until its weight is constant. The yield of crude acid is 6.9–7.2 g. (92–96%). It melts at 210–215° (dec.) (Note 14).

Twelve milliliters of water for each gram of the crude acid

(83–86 ml.) is added to the flask, which is then attached to a reflux condenser and immersed in an oil bath at 150°. After 10–20 minutes of boiling, a clear pale-yellow solution is obtained. This is filtered through a fluted filter into an Erlenmeyer flask. After crystallization has started, 8.3–8.6 ml. of 12*N* hydrochloric acid (1.2 ml. of acid for each gram of crude acid) is added, and the mixture is allowed to cool slowly to room temperature, during which period it is occasionally agitated. Crystallization is completed by keeping the flask in a refrigerator for at least 10 hours. The product is separated by suction filtration and washed with a small amount of ice water. The purified *p*-hydroxyphenylpyruvic acid weighs 4.4–4.7 g. (59–63%) and melts at 216–218° (dec.) (Notes 14 and 15).

2. Notes

1. The *p*-hydroxybenzaldehyde used was a commercial product (practical grade) melting at 114–117°.

2. Hydantoin can be prepared in a variety of ways, notably from glycine² or ethyl aminoacetate³ and potassium cyanate. The checkers used Eastman Kodak “white label” hydantoin.

3. Because of the viscous nature of the reaction mixture, which sometimes shows a tendency to crystallize, this is a slow process, but a mechanical stirrer is not required.

4. The checkers found that three or four cold-water washes are sufficient to wash the precipitate to neutral pH.

5. Further purification may be achieved by crystallization from acetic acid (50 ml. per g.). A product melting at 315° (dec.) is obtained.

6. The inlet tube, preferably in the center neck, is placed in such a way that it nearly touches the bottom of the flask. Thereby nitrogen bubbles effect some agitation of the reaction mixture and prevent bumping of the boiling solution.

7. *p*-Hydroxyphenylpyruvic acid is rapidly oxidized in alkaline solution. Commercially available compressed nitrogen may be used if the gas is further purified by passage through an alkaline solution of pyrogallol (45 g. of pyrogallol dissolved in 300 ml. of 50% sodium hydroxide solution).

8. This should be done in a hood because ammonia is evolved.

9. The purpose of the first extraction is to remove phenolic impurities. Care should be taken to adjust to the proper pH range (6-7). At this pH the solution changes in color from orange to yellow. A small amount of a flocculent precipitate is formed, but, to avoid longer contact of the solution with air, it is not filtered off.

10. A convenient type of extractor is described in *Organic Syntheses*.⁴ The submitter improved the efficiency of the extractor by stirring the aqueous phase with a magnetic stirrer. The inner tube had no filter on the lower end of it and was suspended so that this end was about 1 cm. above the magnetic stirring bar. Tests show that magnetic stirring of the aqueous phase increases the speed of extraction by a factor of 2 to 3. It is convenient to use an extractor of such size that the same apparatus can be used for both extractions. A greater volume of solution must be handled in the second extraction than in the first because of the addition of hydrochloric acid.

11. Evaporating the ethereal solution yields not more than 0.3 g. of brown tarry material consisting mostly of impure *p*-hydroxybenzaldehyde.

12. Carbon dioxide and fumes of ether are evolved during the addition of the acid. The solution is stirred by means of a glass rod until the foaming ceases.

13. This is a slow process, and the extraction time depends on the type of extractor used. With stirring as described in Note 10, practically quantitative extraction of *p*-hydroxyphenylpyruvic acid can be achieved within 6 hours. Extremely long extraction times may cause decomposition of the product.

14. The checkers observed a decomposition point of 198-202° for the crude acid, 211-214° for the purified acid.

15. A second crystallization from 10 parts of water raises the melting point of the acid to 220°. Any prolonged contact of the hot solution with air will cause some decomposition, notably the formation of traces of *p*-hydroxybenzaldehyde. The checkers preferred crystallization from 10 parts of glacial acetic acid and 10 parts of 12*N* hydrochloric acid,⁶ from which solvent a white product was recovered in 75% yield; m.p. 220° (dec.).

The purity of the *p*-hydroxyphenylpyruvic acid may be

checked by paper chromatography. By the ascending method on Schleicher and Schüll paper No. 2043b and *n*-butanol-acetic acid-water (4:1:1) as solvent, the following R_f values are obtained: *p*-hydroxyphenylpyruvic acid, 0.71; *p*-hydroxybenzaldehyde, 0.85. Sprays: 2,4-dinitrophenylhydrazine (0.2% in 2*N* hydrochloric acid) and Folin-Denis reagent.⁶

3. Methods of Preparation

p-Hydroxyphenylpyruvic acid has been prepared by alkaline hydrolysis of the azlactone of α -benzoylamino-*p*-acetoxycinnamic acid⁷ and by a two-step hydrolysis of the azlactone of α -acetamino-*p*-acetoxycinnamic acid.⁸ *p*-Hydroxyphenylpyruvic acid has also been prepared by alkaline hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin.⁹ The procedure described here is adapted from published directions for the preparation of *p*-hydroxyphenylpyruvic-3-¹⁴C acid.⁵ 5-(*p*-Hydroxybenzal)hydantoin is prepared according to the method of Boyd and Robson.¹⁰

4. Merits of the Preparation

p-Hydroxyphenylpyruvic acid plays an important role in the biogenesis of compounds with a phenylpropane skeleton, and it has been used as substrate in several enzyme studies. Published procedures for its preparation are unsatisfactory in many ways. The alkaline hydrolysis of the azlactone of α -benzoylamino-*p*-acetoxycinnamic acid⁷ makes necessary a tedious separation of the resulting benzoic acid, and the yield is only 34% based on *p*-hydroxybenzaldehyde. The hydrolysis of 5-(*p*-hydroxybenzal)-3-phenylhydantoin⁹ requires a separation of phenylurea. Finally, the two-step cleavage of the azlactone of α -acetamino-*p*-acetoxycinnamic acid⁸ does not proceed easily, and impure products are obtained. In applying this procedure to the synthesis of a carboxyl-labeled *p*-hydroxyphenylpyruvic acid, the overall yield was only 9%.¹¹ It must be kept in mind that any prolonged isolation procedure will cause some decomposition of this sensitive compound.

The method of preparing *p*-hydroxyphenylpyruvic acid pre-

sented here has the advantage that only volatile by-products, ammonia and carbon dioxide, are formed. Therefore the compound can be obtained in high purity and good yield. There are no difficulties in decreasing the amounts of starting materials to the millimole scale, as shown by the application of this procedure to the preparation of labeled *p*-hydroxyphenylpyruvic acid.⁵

Finally, this method is of general utility, for alkaline cleavage of analogously substituted hydantoins has given a series of substituted phenylpyruvic acids.¹²

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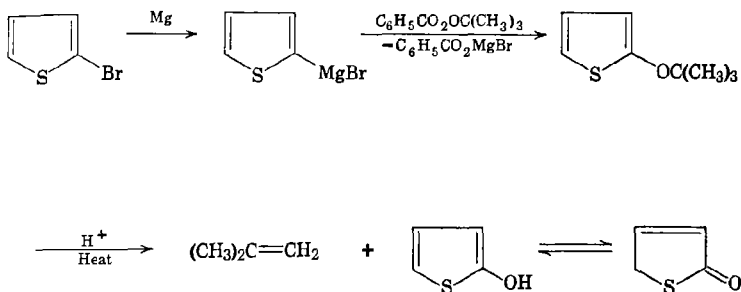
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2-HYDROXYTHIOPHENE

[Thiophene-2-ol and 2(5H)-thiophenone]

Submitted by C. FRISELL and S.-O. LAWESSON.¹

Checked by R. M. SCRIBNER, C. G. MCKAY and B. C. MCKUSICK.

1. Procedure

A. *2-tert-Butoxythiophene*. A dry 1-l. three-necked flask is fitted with a mechanical stirrer (Note 1), a reflux condenser having a take-off attachment, and a 250-ml. dropping funnel with a pressure-equalizing side tube.² A nitrogen-inlet tube is connected to the top of the condenser, and a T-tube branch of this is led to a mercury valve. The latter consists of a U-tube the bend of which is just filled with mercury.

Ten grams (0.41 g. atom) of magnesium turnings (Note 2) is placed in the flask and covered with 200 ml. of dry ether. Ten milliliters of a solution of 65.2 g. (0.40 mole) of 2-bromothiophene in 60 ml. of dry ether is added, the Grignard reaction is started by gently warming the reaction flask, and the remainder of the solution is added dropwise during 45 minutes. The mixture is stirred for 3.5 hours, the last 15 minutes under reflux. The Grignard reagent is cooled to 0–5° by immersing the flask in ice water. *tert*-Butyl perbenzoate (62 g., 56 ml., 0.32 mole) (Note 3) in 100 ml. of dry ether is added dropwise during 45 minutes to the stirred ice-cooled mixture. The reaction mixture is stirred over-

night, poured into ice water, and acidified with concentrated hydrochloric acid. The two phases are separated, and the water phase is twice extracted with ether. The combined ether solutions are extracted with three 60-ml. portions of 2*N* sodium hydroxide solution (Note 4), washed until neutral with water, dried over anhydrous sodium sulfate, and transferred to a distillation flask equipped with a Vigreux column. *Caution! The ether extract should not be distilled unless a test shows that peroxides are absent (Note 5).* The ether is distilled off at atmospheric pressure, and the residual oil is distilled under reduced pressure to give 35–38 g. (70–76%) of 2-*tert*-butoxythiophene, b.p. 64–66°/13 mm., n_D^{20} 1.4991.

B. *2-Hydroxythiophene*. The 2-*tert*-butoxythiophene obtained in Step A is placed in a distillation flask equipped with a short Vigreux column and a capillary inlet for nitrogen, and 0.1 g. of *p*-toluenesulfonic acid is added. The apparatus is placed in an oil bath at 155°. Decomposition begins immediately. After 5–10 minutes the oil bath is removed, and the distillation assembly is connected to a water pump (Note 6). 2-Hydroxythiophene is distilled under reduced pressure, nitrogen gas being drawn through the capillary during the whole procedure (Note 7). 2-Hydroxythiophene is collected at 91–93°/13 mm.; yield 20–23 g. (89–94%); n_D^{20} 1.5613 (Note 8).

2. Notes

1. Although a mercury seal is preferable, a rubber tube lubricated with glycerol is an adequate seal.

2. Common laboratory magnesium is as satisfactory as extremely pure sublimed magnesium.

3. *tert*-Butyl perbenzoate is supplied by Lucidol Division, Wallace and Tiernan, Inc., Buffalo, New York, and Light and Co., Colnbrook, Bucks, England.

4. Acidification of the basic solution gives 29–32 g. (80–88%) of benzoic acid if the reaction has proceeded properly.

5. To make a peroxide test, place a few milligrams of sodium iodide, a trace of ferric chloride, and 2–3 ml. of glacial acetic acid in a test tube and carefully add 1–2 ml. of the ether solution.

When unconsumed perbenzoate is present, a yellow ring is immediately formed between the two phases. *If this test indicates the presence of peroxide, the extract should not be concentrated and distilled until it has been extracted first with a solution of potassium iodide in acetic acid to remove peroxide and then with aqueous sodium thiosulfate to remove iodine.*

6. The decomposition is considered to be complete when the pressure is constant.

7. 2-Hydroxythiophene resinifies on prolonged exposure to air.

8. It has recently been shown that 2-hydroxythiophene exists mainly as 2(5H)-thiophenone at room temperature.³

3. Methods of Preparation

The procedure described is essentially that of Lawesson and Frisell.⁴ 2-Hydroxythiophene has been prepared in low yields by Hurd and Kreuz⁵ from 2-thienylmagnesium bromide and oxygen in the presence of excess isopropylmagnesium bromide.

4. Merits of the Preparation

The first step of the procedure illustrates a general way of preparing aryl *tert*-butyl ethers.^{4,6} The second step is the best way to prepare 2-hydroxythiophene, inasmuch as the yield is good and *tert*-butyl perbenzoate is a readily available perester that is relatively stable. The same procedure has been used to convert several other haloaromatic compounds to hydroxyaromatic compounds in good yield⁴ and is probably quite general.

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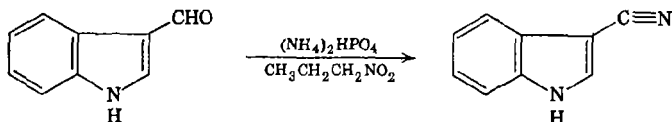
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INDOLE-3-CARBONITRILE



Submitted by H. M. BLATTER, H. LUKASZEWSKI, and G. DE STEVENS.¹

Checked by WAYLAND E. NOLAND and KENT R. RUSH.

1. Procedure

A mixture of 1.44 g. (0.0099 mole) of indole-3-carboxaldehyde,² 7.0 g. (0.053 mole) of diammonium hydrogen phosphate, 30 g. (30 ml., 0.34 mole) of 1-nitropropane, and 10 ml. of glacial acetic acid is refluxed for 12.5 hours. During the reflux period the pale-yellow mixture becomes dark red. The volatile reactants and solvent are removed under reduced pressure, and an excess of water is then added to the dark residue. After a short time, crude indole-3-carbonitrile precipitates rapidly. It is separated by filtration and dried under reduced pressure; weight 1.20–1.34 g. (85–95%). Crystallization from acetone-hexane, with decolorization by activated carbon, yields 0.68–0.89 g. (48–63%) of fairly pure indole-3-carbonitrile, m.p. 179.5–182.5° (Note 1).

2. Note

1. The checkers obtained pure indole-3-carbonitrile, m.p. 182–184°, by subliming the product at a pressure of 1.5 mm. (bath temperature 165–170°) and recrystallizing the sublimate from a mixture of acetone and light petroleum ether. The recovery was 84%.

3. Methods of Preparation

Indole-3-carbonitrile has been prepared by the dehydration of indole-3-carboxaldehyde oxime,³⁻⁵ indole-3-glyoxalic acid oxime,^{4,6} or indole-3-carboxamide;³ by the action of cyanogen

chloride on indolylmagnesium iodide;⁶ by the reaction of isoamyl formate with *o*-aminobenzyl cyanide in the presence of metallic sodium;^{7,8} by mild basic hydrolysis of 1-acetylindole-3-carbonitrile;⁷ and by the present method.⁹

4. Merits of the Preparation

This synthetic process is applicable to the preparation of other aromatic nitriles from aldehydes. The submitters have used it to prepare 5-bromoindole-3-carbonitrile, 7-azaindole-3-carbonitrile, *p*-chlorobenzonitrile, 3,4,5-trimethoxybenzonitrile, and *p*-N,N-dimethylaminobenzonitrile.⁹ There are several advantages to its use. They include (a) readily available and inexpensive reagents, (b) a simple, time-saving procedure, and (c) fair to good yields of nitrile obtained by a *one-step* method.

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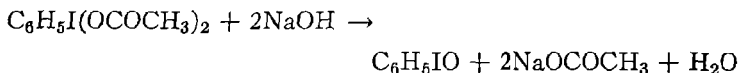
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IODOSOBENZENE

(Benzene, iodoso-)



Submitted by H. SALTZMAN and J. G. SHAREFKIN.¹

Checked by MELVIN S. NEWMAN and NARINDER GILL.

1. Procedure

Caution! This compound explodes if heated to 210°.

Finely ground iodosobenzene diacetate² (32.2 g., 0.10 mole) is placed in a 250-ml. beaker, and 150 ml. of 3*N* sodium hydroxide is added over a 5-minute period with vigorous stirring. The lumps of solid that form are macerated with a stirring rod or spatula for 15 minutes, and the reaction mixture stands for an additional 45 minutes to complete the reaction. One hundred milliliters of water is added, the mixture is stirred vigorously, and the crude, solid iodosobenzene is collected on a Büchner funnel. The wet solid is returned to the beaker and macerated in 200 ml. of water. The solid is again collected on the Büchner funnel, washed there with 200 ml. of water, and dried by maintaining suction. Final purification is effected by macerating the dried solid in 75 ml. of chloroform in a beaker. The iodosobenzene is separated by filtration (Note 1) and air-dried; weight 18.7–20.5 g. (85–93%); m.p. 210° (*Caution! Explodes!*). Iodometric titration³ shows the product to be more than 99% pure (Note 2).

2. Notes

1. The filtrate yields unreacted diacetate on evaporation.
2. The purity of the iodosobenzene depends on the purity of the diacetate used.

3. Methods of Preparation

Iodosobenzene has been prepared by the action of sodium or potassium hydroxide solution on iodobenzene dichloride^{3,4} and by addition of water to the dichloride.⁵

4. Merits of the Preparation

This method of preparing iodosobenzene is preferable to older ones based on iodosobenzene dichloride because iodosobenzene diacetate² is more stable and more conveniently prepared than the dichloride³ and the overall yield is greater (75% versus 54%).

The procedure seems to be a general way of preparing iodosoarenes with electron-donating substituents, for the submitters have used it to obtain good yields of *o*-, *m*- and *p*-iodosotoluene, 2- and 4-iodoso-*m*-xylene, 2-iodoso-*p*-xylene, *o*-iodosophenetole, and 4-iodosobiphenyl.

Iodosoarenes are useful in the preparation of iodonium salts, $\text{Ar}_2\text{I}^+\text{X}^-$.⁶

¹ Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn 10, New York.

² J. G. Sharefkin and H. Saltzman, this volume, p. 62.

³ H. J. Lucas, E. R. Kennedy, and M. W. Forino, *Org. Syntheses*, Coll. Vol. **3**, 483 (1955).

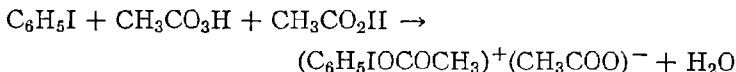
⁴ C. Willgerodt, *Chem. Ber.*, **25**, 3494 (1892); **26**, 357, 1802 (1893); P. Askenasy and V. Meyer, *Chem. Ber.*, **26**, 1354 (1893); C. Hartmann and V. Meyer, *Chem. Ber.*, **27**, 502 (1894).

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⁶ F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *J. Am. Chem. Soc.*, **81**, 343 (1959); C. Hartmann and V. Meyer, *Chem. Ber.*, **27**, 426, 504 (1894).

IODOSOBENZENE DIACETATE

(Benzene, iodoso-, diacetate)

Submitted by J. G. SHAREFKIN and H. SALTZMAN,¹

Checked by J. DIEKMANN and B. C. McKUSICK.

1. Procedure

Caution! Avoid inhaling the vapor of peracetic acid or allowing the liquid to come into contact with the skin. The reaction is best carried out in a hood (Note 1).

The apparatus consists of a 200-ml. beaker equipped with a magnetic stirrer or any other type suitable for stirring a small volume of liquid. The flask is charged with 20.4 g. (0.10 mole) of iodobenzene² and is immersed in a water bath maintained at 30° (Note 2). Thirty-six grams (31 ml., 0.24 mole) of commercial 40% peracetic acid (Note 3) is added dropwise to the well-stirred iodobenzene over a period of 30–40 minutes. Stirring is continued for another 20 minutes at a bath temperature of 30°, during which time a homogeneous yellow solution is formed. Crystallization of iodosobenzene diacetate may begin during this period.

The beaker is chilled in an ice bath for 1 hour. The crystalline diacetate that separates is collected on a Büchner funnel and washed with three 20-ml. portions of cold water. After drying for 30 minutes on the funnel with suction, the diacetate is dried overnight in a vacuum desiccator containing calcium chloride (Note 4). The dried diacetate weighs 26.7–29.3 g. (83–91%) and melts at 158–159° with decomposition. The purity of the diacetate, determined by the titration method of Lucas, Kennedy, and Formo,³ is 97–98%, which is good enough for most purposes. The purity can be increased to 99–100% by a recrystallization from 5*M* acetic acid.

2. Notes

1. Rubber gloves should be worn when handling vessels containing peracetic acid, for traces of the liquid can cause severe irritation. Skin that has come into contact with peracetic acid should be washed immediately and treated with sodium bicarbonate. Details for the safe handling of peracetic acid are found in Bulletin 4 supplied by Buffalo Electrochemical Corp.

2. Appreciable amounts of iodoxybenzene are formed if the temperature of the bath is allowed to go above 30° or if the addition of peracetic acid is faster than indicated.

3. Satisfactory 40% peracetic acid is obtainable from Buffalo Electrochemical Corp., Food Machinery and Chemical Corp., Buffalo, New York. The specifications given by the manufacturer for its composition are: peracetic acid, 40%; hydrogen peroxide, 5%; acetic acid, 39%; sulfuric acid, 1%; water, 15%. Its density is 1.15 g. per ml.

A fresh sample of this 40% peracetic acid contains about 1.54 equivalents, or 0.77 mole, of peroxide per 100 ml. of solution, corresponding to 1.34 equivalents per 100 g. The concentration can be determined by treating the peroxide solution with potassium iodide and titrating the liberated iodine with standard sodium thiosulfate. The concentration of peroxide in peracetic acid decreases somewhat on long standing and should be checked before the peracetic acid is used. The yield of diacetate is lowered if the concentration of the peroxide is less than 1.0 equivalent per 100 g. of peracetic acid. The total amount of peroxide used should be 2.4 moles, or 4.8 equivalents, for each mole of iodosobenzene.

4. The surface of the diacetate may become yellow during the drying, but this does not affect its usefulness for most purposes.

3. Methods of Preparation

Willgerodt⁴ prepared iodosobenzene diacetate by adding chlorine to iodobenzene and hydrolyzing the dichloride to iodosobenzene, which was then reacted with acetic acid. Pausacker⁵ used this method to synthesize a number of analogs but found it

inferior to his modification of the method of Böeseken and Schneider ⁶ in which iodobenzene is treated with 30% hydrogen peroxide and acetic anhydride. Arbusov ⁷ obtained the diacetate in 79% yield by the action of a mixture of peracetic and acetic acids on iodobenzene. Quantitative yields of the diacetate have been claimed for the reaction of iodobenzene dichloride with lead tetraacetate in glacial acetic acid containing 10% acetic anhydride, followed by precipitation of the lead as the chloride.⁸

4. Merits of the Preparation

Iodosobenzene diacetate is best prepared by the action of peracetic acid and acetic acid on iodobenzene. The present procedure is superior to earlier ones ⁵⁻⁸ because it uses inexpensive, commercially available peracetic acid, is faster, and gives higher yields. The procedure seems general for aryl iodides with electron-releasing substituents, for the submitters have obtained good yields of diacetates from *o*-, *m*- and *p*-iodotoluene, 2- and 4-iodo-*m*-xylene, 2-iodo-*p*-xylene, *o*-iodophenetole, and 4-iodobiphenyl.

Iodosobenzene diacetate is used as a reagent for the preparation of glycol diacetates from olefins,⁹ for the oxidation of aromatic amines to corresponding azo compounds,¹⁰ for the ring acetylation of N-arylacetamides,¹¹ for oxidation of some phenols to phenyl ethers,¹² and as a coupling agent in the preparation of iodonium salts.¹³ Its hydrolysis to iodosobenzene constitutes the best synthesis of that compound.¹⁴

¹ Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn 10, New York.

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⁶ J. Böeseken and G. C. C. Schneider, *J. Prakt. Chem.*, **131**, 285 (1931).

⁷ B. A. Arbusov, *J. Prakt. Chem.*, **131**, 351 (1931).

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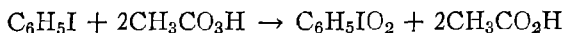
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¹⁴ H. Saltzman and J. G. Sharefkin, this volume, p. 60.

IODOXYBENZENE

(Benzene, iodoxy-)



Submitted by J. G. SHAREFKIN and H. SALTZMAN.¹

Checked by E. J. COREY and C. P. LILLYA.

1. Procedure

Caution! Avoid inhaling the vapor of peracetic acid or allowing the liquid to come into contact with the skin. The reaction is best carried out in a hood (Note 1). Iodoxybenzene explodes if heated to 230°.

A 500-ml. three-necked flask fitted with reflux condenser, stirrer, and dropping funnel and containing 20.4 g. (0.10 mole) of iodobenzene² is immersed in an oil bath maintained at 35°. Seventy-five grams (65 ml., 0.50 mole) of commercial 40% peracetic acid (Note 1) is added with vigorous stirring over a 30-minute period. Solid may begin to form before all the peracetic acid has been added, but, although this may slow down the stirring, it does not decrease the yield or cause a rise in temperature.

After all the peracetic acid has been added, the reaction mixture is diluted with 80 ml. of water and heated from 35° to 100° over a 20-minute period (Note 2). It is then kept at 100° for 45 minutes. The flask is cooled to 0–5° in an ice bath, and the solid iodoxybenzene is collected on a Büchner funnel and air-dried with suction for 1 hour. Additional material is obtained by concentrating the filtrate to one-fourth of its volume (*Caution! Note 3*). The two crops of crude iodoxybenzene are combined and dried overnight in a desiccator; weight 19.6–20.5 g.; m.p. 230° (*Caution! Explodes!*). Iodometric titration³ shows the purity to be about 94% (Note 4).

Purification of the crude iodoxybenzene is effected by grinding it to a powder in a mortar, macerating it with 70 ml. of chloroform, and separating the solid by filtration. The chloroform extraction is repeated and the solid is dried; weight 17–19 g. (72–80%); purity 99.0–99.9% by iodometric titration.³

2. Notes

1. For a source and the specifications of 40% peracetic acid and precautions in handling it, see Notes 3 and 1 under the preparation of iodosobenzene diacetate, p. 62.

2. If the temperature of the bath is not raised slowly, foaming is difficult to control. Although the gradual rise in temperature causes considerable foaming, the reaction mixture remains within the flask.

3. The filtrate must not be evaporated to dryness because iodoxybenzene explodes when heated.

4. The major by-products in this reaction are iodobenzene and iodosobenzene diacetate. An excess of 20 ml. of peracetic acid over the 65 ml. recommended results in an increase in the amount of iodobenzene. Both impurities are removed from the product by washing with chloroform.

3. Methods of Preparation

Iodoxybenzene has been prepared by the disproportionation of iodosobenzene,^{4–6} by oxidation of iodosobenzene with hypochlorous acid or bleaching powder,⁷ and by oxidation of iodobenzene with hypochlorous acid or with sodium hydroxide and bromine.⁸ Other oxidizing agents used with iodobenzene include air,⁹ chlorine in pyridine,⁹ Caro's acid,^{10,11} concentrated chloric acid,¹² and peracetic acid solution.¹³ Hypochlorite oxidation of iodobenzene dichloride has also been employed.¹⁴

4. Merits of the Preparation

This one-step method of preparing iodoxybenzene is preferable to earlier methods because it is simpler and the yield is substantially higher. The procedure seems general for iodoxyarenes,

at least those with electron-releasing substituents, for the submitters have used it to obtain good yields of *o*-, *m*- and *p*-iodoxytoluene, 2- and 4-iodoxy-*m*-xylene, 2-iodoxy-*p*-xylene, *o*-iodoxyphenetole, 4-iodoxybiphenyl, and *o*-iodoxybenzoic acid.

Iodoxyarenes are useful in the preparation of iodonium salts, $\text{Ar}_2\text{I}^+\text{X}^-$.¹⁵

¹ Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn 10, New York.

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³ C. Willgerodt, *Chem. Ber.*, **25**, 3500 (1892); **26**, 358 (1893).

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⁹ G. Ortoleva, *Chem. Zentr.*, **1900**, 723.

¹⁰ E. Bamberger and A. Hill, *Chem. Ber.*, **33**, 534 (1900).

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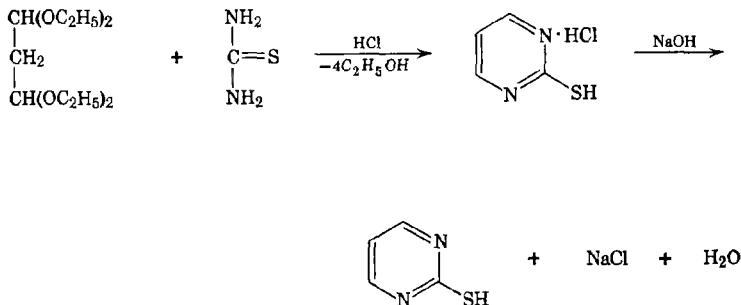
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¹⁵ C. Hartman and V. Meyer, *Chem. Ber.*, **27**, 504 (1894).

2-MERCAPTOPYRIMIDINE

(2-Pyrimidinethiol)



Submitted by DONALD G. CROSBY, ROBERT V. BERTHOLD,
and HERBERT E. JOHNSON.¹

Checked by B. BELLIN, J. L. GIBBS, and V. BOEKELHEIDE.

1. Procedure

A. *2-Mercaptopyrimidine hydrochloride*. Thiourea (61 g., 0.80 mole) and 600 ml. of ethyl alcohol (Note 1) are placed in a 2-l. three-necked flask equipped with a sealed mechanical stirrer, a reflux condenser, and a stopper. The stirrer is started, and 200 ml. of concentrated hydrochloric acid is added in one portion through the open neck. After several minutes, when the warm mixture has become homogeneous, 176 g. (0.80 mole) of commercial-grade 1,1,3,3-tetraethoxypropane (Note 2) is added rapidly, the open neck is stoppered, and the yellow solution is boiled for about 1 hour with continuous stirring. During this period the reaction mixture darkens in color and the product separates (Note 3).

The reaction mixture is chilled to about 10° by immersing it in an ice bath for about 30 minutes, and the yellow crystalline precipitate is collected on a Büchner funnel. It is then washed with 100 ml. of cold alcohol and air-dried at room temperature. The yield of 2-mercaptopyrimidine hydrochloride is 71–76 g.

(60–64%). The product is pure enough for most purposes (Note 4), but it may be recrystallized by dissolving it in 12*N* hydrochloric acid (10 ml. per gram of solid) at about 75°, filtering the hot solution through glass wool or a sintered glass filter, chilling the filtrate in ice, and collecting the golden-yellow crystals on a sintered glass filter. Recovery is 60–65% (Note 5).

B. 2-Mercaptopyrimidine. Crude 2-mercaptopyrimidine hydrochloride (25 g., 0.17 mole) is suspended in 50 ml. of water in a beaker and stirred rapidly while a 20% aqueous solution of sodium hydroxide (about 27 ml.) is added until the pH of the mixture is 7–8 (Note 6). The precipitated solid is collected on a Büchner funnel and washed on the funnel with 50 ml. of cold water. The damp product is dissolved by heating it in a mixture of 300 ml. of water and 300 ml. of alcohol on the steam bath, and the hot solution is filtered through a fluted paper and allowed to cool slowly to room temperature. The crystals of 2-mercaptopyrimidine are collected, washed with about 50 ml. of the aqueous alcohol, and dried either at room temperature overnight or for several hours in an oven at 110°. The yield is 15–16 g. (80–85%) of yellow needles, m.p. 218–219° (sealed tube).

2. Notes

1. Either commercial absolute alcohol or the 95% grade may be used.

2. 1,1,3,3-Tetraethoxypropane is available from Kay-Fries Chemicals, Inc., New York 16, New York, or from Distillation Products Industries, Rochester 3, New York, and may be used without further purification.

3. Longer boiling does not affect the yield but causes the product to be somewhat dark-colored. A shorter heating period or lack of mechanical stirring decreases the yield.

4. Electrometric titration shows the purity to be at least 95%. The product does not melt below 300°.

5. If concentrated sulfuric acid is substituted for the hydrochloric acid in the procedure, 2-mercaptopyrimidine bisulfate is obtained in about 50% yield. Recrystallization from aqueous acetic acid provides the bisulfate as yellow needles, m.p. 186–

186.5°. (*Anal.* Calcd. for $C_4H_6N_2O_4S_2$: C, 22.9; H, 2.9. Found: C, 23.1; H, 2.9.)

6. pH indicator paper may be used, or the solution may be made weakly basic to litmus. Excess base dissolves the product and should be avoided.

3. Methods of Preparation

The synthesis of 2-substituted pyrimidines from 1,3-dicarbonyl compounds and urea derivatives was first described by Evans² and was later improved by Hunt, McOmie, and Sayer³ for the preparation of 2-mercapto-4,6-dimethylpyrimidine. Burness⁴ employed 3-ketobutyr aldehyde acetal in this procedure to give 2-mercapto-4-methylpyrimidine. 2-Mercaptopyrimidine has been prepared from 1,1,3,3-tetraethoxypropane and thiourea by variations of this basic method^{3,5,6} as well as by the reaction of 2-chloropyrimidine with thiourea⁷ or sodium hydrosulfide.⁸

4. Merits of the Preparation

This preparation describes a convenient and general method of synthesis of substituted pyrimidines from compounds containing a β -dicarbonyl group, either intact or as the corresponding ketal. The usefulness of the 2-mercaptopyrimidines is enhanced by the ease of removal of the mercapto group by desulfurization⁹ or oxidation¹⁰ and its replacement by other functional groups.¹⁰

¹ Research Department, Union Carbide Chemicals Company, South Charleston, West Virginia.

² P. N. Evans, *J. Prakt. Chem.*, [2] 48, 489 (1893).

³ R. R. Hunt, J. F. W. McOmie, and E. R. Sayer *J. Chem. Soc.*, 1959, 525.

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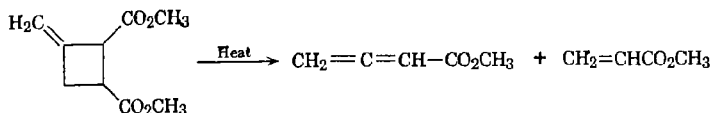
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METHYL BUTADIENOATE

(Butadienoic acid, methyl ester)

Submitted by H. B. STEVENSON and W. H. SHARKEY.^{1a}Checked by R. D. BIRKENMEYER, W. E. RUSSEY, and F. KAGAN.^{1b}

1. Procedure

A "Vycor" tube 550 mm. long and 25 mm. in outside diameter is packed for 500 mm. of its length with 6-mm. x 6-mm. quartz rings and mounted vertically so that the upper section is encased in a tube furnace 150 mm. long and the lower section is encased in a tube furnace 300 mm. long. The upper furnace, which serves as a preheater, is monitored by a thermocouple placed between the tube and the furnace heating elements. The temperature of the lower furnace is monitored by a thermocouple located in the center of the lower packed section. The upper end of the pyrolysis tube is fitted with a Y-tube carrying the thermocouple well and a graduated addition funnel with a pressure-equalizing arm. The lower end is attached through one 500-ml. trap and two 200-ml. traps, each immersed in a mixture of solid carbon dioxide and acetone, to a regulated vacuum source. One gram of hydroquinone is placed in the first trap.

The pyrolysis tube is flushed with nitrogen, the lower section is heated to 600° and the upper section to 300° (Note 1), and the pressure is regulated at 25 mm. Then 184 g. (1.00 mole) (Note 2) of dimethyl 3-methylenecyclobutane-1,2-dicarboxylate² is admitted over a period of 3 hours (Note 3). The product, which amounts to 172–177 g., collects in the traps. It is distilled through a 13-mm. x 1.2-m. Nester spinning-band still.³ First

there is 41–47 g. (48–55%) of methyl acrylate, n_D^{25} 1.4010, b.p. 34–36°/150 mm., then 39–43 g. (40–44%) of methyl butadienoate, n_D^{25} 1.4635 (Note 4), b.p. 59–60°/52 mm. or 48–49°/26 mm. By continuing the distillation, 20–30 g. of starting material, b.p. 125–150°/25 mm., can be recovered.

2. Notes

1. The temperature of the lower section is quite critical and should be maintained within the range 590–610°. However, the preheater section is needed only to volatilize the ester, so any temperature between 200° and 400° is satisfactory.

2. Since an estimated 3–5 g. of carbon is deposited in the tube during the pyrolysis, it is advisable to pyrolyze only 1 mole of ester at a time and to burn out the carbon with a slow stream of air at 600° between pyrolyses.

3. The space velocity is approximately 125 l. of standard gas per l. of free space per hour, and the contact time is approximately 0.3 second.

4. The checkers used a 10-mm. x 0.76-m. Nester spinning band still and obtained material having n_D^{25} 1.4620 that could not be purified by redistillation. Analysis by vapor-phase chromatography (silicone gum rubber, 20% w/w on firebrick, 120-cm. x 6-mm. outside diameter column at 125°) showed this material to be 95% methyl butadienoate contaminated by small amounts of two other materials.

3. Methods of Preparation

The method used is described by Drysdale, Stevenson, and Sharkey.⁴ The methyl ester of butadienoic acid has not been described previously, but the free acid contaminated by 2-butyric acid has been prepared by Wotiz, Matthews, and Lieb⁵ by carbonation of propargylmagnesium bromide. Ethyl butadienoate has been prepared by Eglinton, Jones, Mansfield, and Whiting⁶ by alkali-catalyzed isomerization of ethyl 3-butyrate prepared from 3-butyrol by chromic acid oxidation and esterification.

4. Merits of the Preparation

This procedure gives a product free of acetylenic groups. It illustrates the synthesis of an olefinic compound by cracking a cyclobutane into two fragments.

^{1a} Contribution No. 568 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

^{1b} Upjohn Co., Kalamazoo, Michigan.

² H. B. Stevenson, H. N. Cripps and J. K. Williams, this volume, p. 27.

³ R. G. Nester, *Anal. Chem.*, **28**, 278 (1956).

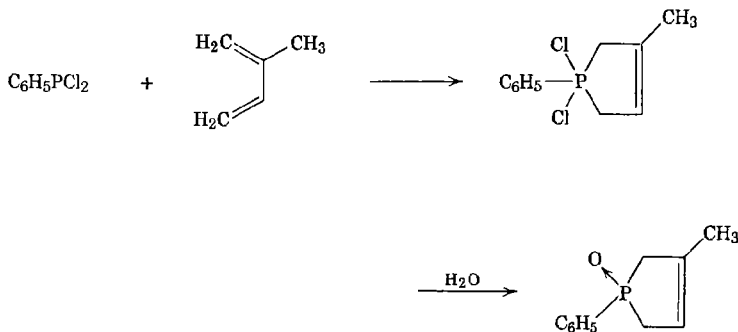
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3-METHYL-1-PHENYL-1-PHOSPHA-3-CYCLOPENTENE 1-OXIDE

(3-Phospholene, 3-methyl-1-phenyl-, 1-oxide)



Submitted by W. B. McCORMACK.¹

Checked by S. N. LEWIS and W. D. EMMONS.

1. Procedure

A. *1,1-Dichloro-1-phenyl-3-methyl-1-phospha-3-cyclopentene*. A dry 1-l. suction flask (Note 1) is charged with 179 g. (1.00 mole)

of dichlorophenylphosphine (n_D^{25} 1.592; Note 2), 300 ml. (about 204 g., 3.0 moles) of commercial isoprene (Note 3), and 2.0 g. of Ionol* (Note 4). The flask is then stoppered, the side arm is sealed with tubing and a clamp, and the homogeneous solution is allowed to sit at room temperature in the back of a hood for 5–7 days. White solid is usually apparent within 2–4 hours, and after the reaction period the liquid phase is full of a white crystalline adduct, 1,1-dichloro-1-phenyl-3-methyl-1-phospha-3-cyclopentene. The granular adduct is crushed, slurried with petroleum ether, collected on a sintered glass Büchner funnel, and washed with petroleum ether; exposure to moisture of the air is minimized by covering the funnel with a clock glass (Note 5).

B. *3-Methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide*. The adduct is hydrolyzed by stirring it into 700 ml. of ice water, and stirring is continued until essentially all of it is in solution (Note 6). The total amount of acid in the solution is determined by titrating an aliquot, and the solution is nearly neutralized by slow addition of about 93% of the theoretical amount of 30% sodium hydroxide with good stirring and sufficient ice to keep the temperature below 25°. The solution generally contains about 1.62 equivalents of acid, which calls for 150 ml. (1.50 equivalents) of 30% sodium hydroxide. The pH is then adjusted to 6.5 with sodium bicarbonate solution (Note 7). After saturation of the aqueous solution with sodium chloride, the product is extracted with three 250-ml. portions of chloroform. The chloroform extracts are combined, dried briefly over calcium sulfate, filtered, and concentrated at atmospheric pressure until the temperature of the liquid in the distillation flask is 130°. The residual liquid is fractionated through a 30-cm. packed column. A water aspirator is used initially to strip small amounts of low boilers at 100° (Note 8), and then a mechanical pump is used. There is a fore-shot of a partially solidifying oil, weight 2.3 g., b.p. 163–168°/0.6–0.7 mm. Then 110–120 g. (57–63%) of 3-methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide, b.p. 173–174°/0.7 mm., is collected. It is a viscous liquid of a very pale yellow color that solidifies to a white solid, m.p. 60–65° (Note 9). A small amount of residue remains (Note 10).

2. Notes

1. A suction flask provides a strong-walled reactor that is conveniently stored for the reaction period.

2. Material obtained from the Victor Chemical Works is suitable after redistillation.

3. Shell Chemical material (92% minimum purity) was used. It was noted by the checkers that redistilled isoprene gave slightly better yields. The excess isoprene serves both as a solvent and for mass action. Moreover, dichlorophenylphosphine tends to dissolve in the product, and excess isoprene, by extracting the solid, promotes completion of reaction.

4. Ionol® is a commercial antioxidant, 2,6-di-*tert*-butyl-*p*-cresol, manufactured by Shell Chemical Corp. Inhibitors appear to minimize formation of polymeric side products, although with isoprene the effect is often small.

5. Sometimes, as with less pure reagents or on heating, a viscous oil, red to dark in color, will form instead of a white solid. At other times the solid is rather gummy. In these cases, mixing with petroleum ether as much as possible and decanting must suffice.

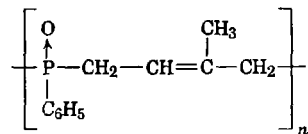
6. On occasion, gelatinous material is apparent; in time it usually dissolves or swells greatly.

7. The product is relatively sensitive to basic conditions, showing both polymerization and addition of water. Therefore alkaline conditions must be avoided. Neutralization serves to convert monophenylphosphinic acid (formed by hydrolysis of unreacted, unextracted dichlorophenylphosphine) to the monosodium salt, thereby preventing its subsequent extraction from water along with the phosphine oxide.

8. The crude mixtures all have strong odors of aromatic phosphines. Some of this odor presumably arises from disproportionation of monophenylphosphinic acid to phenylphosphine. It is recommended that manipulations be carried out with rubber gloves to prevent transfer of these rather durable odors to the skin, and that all equipment be washed with a bleach such as Clorox® before it is taken from the hood.

9. The distilled product can be used as a catalyst, although it usually has a relatively strong phenylphosphine odor. It is quite deliquescent, and it has not been satisfactorily recrystallized. If rigorous purification and deodorization are desired, the product is dissolved in water, a small amount of hydrogen peroxide is added to oxidize the phosphines, the solution is reneutralized, saturated with salt, and extracted with chloroform, and the product is refractionated. One cycle is normally enough. Pure product is essentially odorless, very hygroscopic, and soluble in polar solvents.

10. This residue is mostly the linear copolymer



of nearly 1:1 composition. On occasion it can be present in substantial amounts, especially if higher temperatures are used to increase the reaction rate.

3. Methods of Preparation

3-Methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide has been prepared only as described here.²

4. Merits of the Preparation

The reaction given here has been described before as a general reaction,² and there can be a wide variety of alkyl, aryl, and halo substituents on the diene and phosphorus. Dibromophosphines are appreciably more reactive than dichlorophosphines. If a free-radical catalyst is used instead of an inhibitor, the copolymers can be made in good yield.³ The 1,4-addition of dichlorophosphines to 1,3-dienes is of theoretical interest because of its analogy to the well-known 1,4-addition of sulfur dioxide to 1,3-dienes.

The unsaturated cyclic phosphine oxides are active catalysts

for the conversion of aryl isocyanates to carbodiimides.⁴ The polymeric material³ and the saturated cyclic phosphine oxides⁵ are also catalysts but are less active. The unsaturated cyclic phosphine oxides show properties analogous to those of the unsaturated cyclic sulfones from dienes and sulfur dioxide in that the double bond is quite reactive to basic reagents and relatively resistant to acidic reagents. Physically these cyclic phosphine oxides are stable to over 300°, are very powerful hydrogen bond acceptors, and are excellent solvents for polar materials.

¹ Contribution No. 317, Organic Chemicals Department, E. I. du Pont de Nemours and Co., Wilmington, Delaware

² W. B. McCormack, U.S. Patent 2,663,737 (1953) [C. A., **49**, 7601a (1955)].

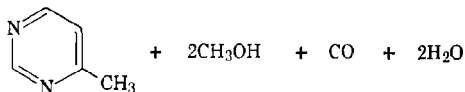
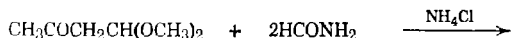
³ W. B. McCormack, U.S. Patent 2,671,079 (1954) [C. A., **48**, 6738c (1954)].

⁴ T. W. Campbell and J. J. Verbanc, U.S. Patent 2,853,473 (1958) [C. A., **53**, 10126e (1959)]; T. W. Campbell and J. J. Monagle, this volume, p. 31

⁵ W. B. McCormack, U.S. Patent 2,663,739 (1953) [C. A., **49**, 7602f (1955)]

4-METHYLPYRIMIDINE

(Pyrimidine, 4-methyl-)



Submitted by H. BREDERECK.¹

Checked by MAX TISHLER, G. A. STEIN, W. F. JANKOWSKI,
and J. TEN BROEKE.

1. Procedure

A 2-l three-necked flask is equipped with a stirrer, a thermometer, an addition funnel, and a wide-bore reflux condenser (Note 1). A second condenser set downward for distillation is connected to the top of the reflux condenser by means of a head provided with a thermometer well. The thermometer well should

be positioned in the connecting head in such a manner that the thermometer gives the temperature at the head of the reflux condenser. *Caution! The flask should be in a hood so that the carbon monoxide evolved cannot be a hazard.*

The three-necked flask is charged with 750 ml. of formamide, 25 ml. of water, and 50 g. of ammonium chloride (Note 2). The mixture is heated to 180–190° in an oil bath, and 400 g. (3.02 moles) of 4,4-dimethoxy-2-butanone (Note 3) is added dropwise with stirring over the course of 6 hours (Note 4). The flow of cooling water in the reflux condenser should be adjusted to a rate such that the methanol and methyl formate formed during the reaction distil out (Note 5). After all the acetal has been added, heating is continued for 1 hour (Note 6). The mixture is allowed to cool and is poured into 1 l. of 1N sodium hydroxide. The resultant solution is extracted with chloroform in a liquid-liquid extractor for 24 hours. The chloroform is separated, dried over sodium sulfate, and removed by distillation through a short column on a steam bath.

The residue is distilled under reduced pressure, and all the distillate boiling at 60–80°/15 mm. is collected (Notes 7 and 8). Pure 4-methylpyrimidine is obtained by redistillation through a short column at atmospheric pressure; b.p. 140–142°; n_D^{25} 1.4936; weight 153–180 g. (54–63%).

2. Notes

1. A wide-bore condenser is employed to prevent clogging of the tube by ammonium salts that may sublime from the reaction mixture (Note 5). A Liebig condenser is most suitable because it can be cleaned from the top with a rod or wire during the reaction.

2. An acidic salt must be present so that the acetal bonds will be hydrolyzed. Other salts, such as ammonium formate, may be substituted for ammonium chloride.

3. 4,4-Dimethoxy-2-butanone from Chemische Werke Huls, Huls, Germany, was used by the submitter. The checkers used 4,4-dimethoxy-2-butanone (practical grade) from Eastman Or-

ganic Chemicals Co., Rochester, New York; it was 95% pure by vapor-phase chromatography.

4. The checkers found that, during the course of the addition, the internal temperature fell from 190° to 140°.

5. The checkers found that, if the temperature at the head of the reflux condenser is kept at 50–55°, no ammonium salts collect in the condenser and, therefore, there is no problem of clogging.

6. The checkers found that the temperature of the reaction mixture remains at 140° during the additional hour of heating.

7. It is advisable to carry out a vacuum distillation prior to the final distillation because the tarry residues obtained by distillation at atmospheric pressure retain a considerable amount of product.

8. The checkers collected their product at 50–70°/30 mm.

3. Methods of Preparation

4-Methylpyrimidine has been obtained by the present method² and by a three-step method that begins with the condensation of acetoacetic ester with urea to give 2,6-dihydroxy-4-methylpyrimidine; the latter is treated with phosphorus oxychloride to give 2,6-dichloro-4-methylpyrimidine, which is reduced by zinc dust and water³ or by catalytic hydrogenolysis.⁴

4. Merits of the Preparation

The present one-step procedure for making 4-methylpyrimidine is simpler and easier than the three-step method used in the past. The present procedure and modifications of it have been used to make a variety of 4- and 4,6-substituted pyrimidines.^{2, 5}

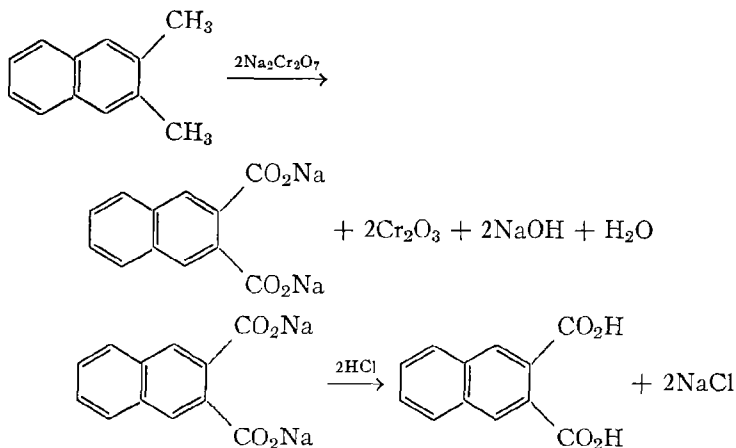
¹ Institut für Organische Chemie, Technische Hochschule, Stuttgart, Germany.

² H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

³ S. Gabriel and J. Colman, *Chem. Ber.*, **32**, 1534 (1899).

⁴ W. Pfeleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 733 (1957).

⁵ H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **91**, 2830 (1958); H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).

2,3-NAPHTHALENEDICARBOXYLIC ACIDSubmitted by LESTER FRIEDMAN.¹

Checked by G. A. BOSWELL and B. C. McKUSICK.

1. Procedure

An autoclave (Note 1) is charged with 200 g. (1.28 moles) of 2,3-dimethylnaphthalene (Note 2), 940 g. (3.14 moles, 23% excess) of sodium dichromate dihydrate, and 1.8 l. of water. The autoclave is closed, heated to 250°, and shaken continuously at this temperature for 18 hours. The autoclave is cooled with continued agitation (Note 3), the pressure is released, and the autoclave is opened. The contents are transferred to a large vessel (Note 4). To effect complete transfer, the autoclave is rinsed with several 500-ml. portions of hot water. Green hydrated chromium oxide in the reaction mixture is separated on a large Büchner funnel and washed with warm water until the filtrate is colorless. The combined filtrates (7–8 l.) are acidified with 1.3 l. of 6*N* hydrochloric acid. The acidified mixture is allowed to

cool to room temperature overnight. The 2,3-naphthalenedicarboxylic acid that has precipitated is collected on a large Büchner funnel, washed with water until the filtrate is colorless, and dried to constant weight in a vacuum oven at 50°/20 mm. or by long standing in air. The 2,3-naphthalenedicarboxylic acid is a white powder; m.p. 239–241°; weight 240–256 g. (87–93%).

2. Notes

1. An autoclave fitted for stirring or shaking is essential for good yields. The submitter used a hydrogenation autoclave of the type supplied by the American Instrument Company, catalog No. 406–21, having a capacity of 3.2 l. The autoclave is shaken by means of a “Bomb Shaker” in which it is placed. If a stirred autoclave or “Magne-Dash” is used, the reaction time can be shortened to 3–5 hours. At 250° the gauge pressure is about 600 lb./in.². The checkers’ yield was 92% in a shaker tube, but only 75% in a rocker tube; the latter yield was raised to 82% by extending the reaction time to 40 hours.

This oxidation does not poison the autoclave for subsequent hydrogenations.

2. Material produced by Ruetgerswerke A. G. is satisfactory. This can be obtained in the United States from Terra Chemicals Inc., New York, New York; Aldrich Chemical Co., Milwaukee 10, Wisconsin; and K and K Laboratories Inc., Jamaica 33, New York.

3. It is convenient to empty the autoclave while the contents are still warm.

4. Commercially available 10-quart polyethylene pails are very satisfactory.

3. Methods of Preparation

2,3-Naphthalenedicarboxylic acid has been prepared by the present method ² and by hydrolysis of 3-cyano-2-naphthoic acid, which is obtainable from 3-amino-2-naphthoic acid by the Sandmeyer reaction.³

4. Merits of the Preparation

This procedure illustrates a general method for the preparation of aromatic carboxylic acids by oxidation of the corresponding alkylarenes.² For example, 2-naphthoic acid (360 g., 93% yield; m.p. 184–185°) was obtained from 2-methylnaphthalene (320 g., 2.25 moles), sodium dichromate (975 g., 3.26 moles, 45% excess), and water (1.8 l.).

2,3-Naphthalenedicarboxylic acid is useful in the synthesis of linear polyacenes,³ 3-halo-2-naphthoic acids,⁴ and 3-amino-2-naphthoic acid.⁴

¹ Chemistry Department, Case Institute of Technology, Cleveland, Ohio.

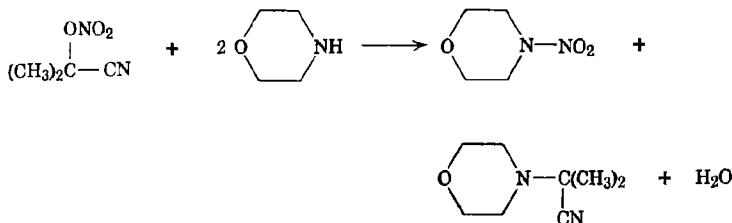
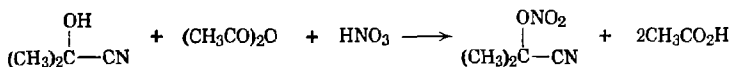
² L. Friedman, D. L. Fishel, and H. Shechter, in press.

³ H. Waldmann and H. Mathiowetz, *Chem. Ber.*, **64**, 1713 (1931).

⁴ L. Friedman, unpublished data.

N-NITROMORPHOLINE

(Morpholine, 4-nitro-)

Submitted by JEREMIAH P. FREEMAN and INELLA G. SHEPARD.¹

Checked by C. G. BOTTOMLEY and B. C. MCKUSICK.

1. Procedure

Caution! The nitrating mixture consisting of fuming nitric acid and acetic anhydride is an extremely active one, and combinations of it and organic materials are potentially explosive. The nitration should be carried out behind adequate safety shields. Acetone cyanohydrin nitrate is moderately explosive (Note 6) and all operations with it, but particularly its distillation, should be carried out behind safety shields.

A. *Acetone cyanohydrin nitrate.* White fuming nitric acid (106 ml., 158 g., 2.3 moles) (Note 1) is added dropwise to 380 ml. (408 g., 4.00 moles) of acetic anhydride at 3–5° contained in a 2-l. three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel and immersed in an ice bath. After the addition, which requires 45 minutes, the mixture is stirred at 5° for 15 minutes (Note 2). Acetone cyanohydrin (92 ml., 85 g., 1.00 mole) (Note 3) is added dropwise to the mixture at 5–10° over a 45-minute period. After the addition, the ice bath is removed and the mixture is allowed to warm to room temperature and is stirred there for 30 minutes. It is then poured into 600 g. of ice

and water, and the resulting mixture is stirred for 90 minutes to dissolve the acetic anhydride.

The mixture is extracted with four 100-ml. portions of methylene chloride. The extracts are combined, washed successively with 100 ml. of water and four 100-ml. portions of 5% sodium carbonate solution (Note 4), and dried over anhydrous magnesium sulfate. The methylene chloride is removed by evaporation at 30–40° under the pressure of a water aspirator, and the residue is distilled through a 30-cm. Vigreux column to yield 85–90 g. (65–69%) (Note 5) of acetone cyanohydrin nitrate (Note 6); b.p. 62–65°/10 mm.; n_D^{20} 1.4170–1.4175 (Note 7).

B. *N-Nitromorpholine*. Morpholine (34.8 g., 0.40 mole) and 26 g. (0.20 mole) of acetone cyanohydrin nitrate are mixed in a 50-ml. round-bottomed flask equipped with a thermometer well. A condenser is attached, and the mixture is heated slowly. At about 60° an exotherm ensues that raises the temperature of the mixture to 110°. The mixture is allowed to cool to 80° and maintained there for 1 hour. It is poured into 200 ml. of 10% hydrochloric acid (*Caution! Do in a hood! Note 8*) and extracted with three 100-ml. portions of methylene chloride (Note 9). The extracts are combined, washed successively with two 100-ml. portions of water, 100 ml. of 10% hydrochloric acid, and 100 ml. of water, and dried over anhydrous magnesium sulfate. The solvent is removed by evaporation on a water aspirator at room temperature to yield a pale-yellow oil (Note 10).

The oil is dissolved in 80 ml. of absolute ethanol. The solution is cooled to 0–5°, causing white crystals of *N*-nitromorpholine to precipitate; weight 15–17 g. (57–64%); m.p. 52–54° (Note 11).

2. Notes

1. This is 90% nitric acid, d. 1.48–1.50. In order to remove dissolved nitrogen oxides from it, 0.5 g. of urea is added and the mixture is air-sparged for 20 minutes. The acid should be colorless before it is added to the acetic anhydride.

2. The nitrating mixture should be colorless at this point. If it is not, 0.5 g. of urea should be added and the mixture air-sparged until colorless.

3. Suitable acetone cyanohydrin can be purchased from the Rohm and Haas Co. and other commercial sources, or it can be prepared as described in *Organic Syntheses*.²

4. Washing with the carbonate solution should be continued until the organic layer is free of acid. Traces of acid may cause extensive decomposition during the distillation.

5. Similar yields were observed in preparations on three times this scale.

6. Acetone cyanohydrin nitrate should be regarded as a moderately explosive material and should be handled carefully and distilled behind a safety shield. For purposes of comparison, the drop-weight sensitivities on the Olin-Mathieson drop-weight tester of three materials are: propyl nitrate, 10 kg.-cm.; acetone cyanohydrin nitrate, 40 kg.-cm.; nitromethane, 60 kg.-cm.

7. The product obtained from this distillation usually contains small amounts of acetone cyanohydrin acetate, as evidenced by an ester carbonyl band at 1740 cm.^{-1} in its infrared spectrum. This material does not interfere with the nitration reactions of the reagent. It may be removed by fractionation through a more efficient column.

8. This operation should be carried out in a good hood because hydrogen cyanide is evolved at this point.

9. The aqueous solution contains α -morpholinoisobutyronitrile in the form of its hydrochloride. It is formed by condensation of morpholine with the acetone and hydrogen cyanide formed in the nitration reaction. It is because of this side reaction that the excess amine is employed.

10. Occasionally this oil solidifies after removal of the last traces of solvent; in these instances it is necessary to warm the ethanol slightly to effect solution.

11. In nitrating amines other than morpholine, particularly on a larger scale, it may be desirable to carry out the reaction in acetonitrile to control the temperature better.³

3. Methods of Preparation

N-Nitromorpholine has been prepared by the oxidation of N-nitrosomorpholine with peroxytrifluoroacetic acid,⁴ by the

chloride ion-catalyzed reaction of nitric acid with morpholine,⁵ by the action of nitric acid and acetic anhydride on N-formylmorpholine,⁶ by the reaction of dinitrogen pentoxide with morpholine,⁷ and by alkaline nitration of morpholine with acetone cyanohydrin nitrate.³

4. Merits of the Preparation

This synthesis of N-nitromorpholine is representative of a rather general reaction for the preparation of both primary and secondary nitramines.³ It represents the simplest process for obtaining both types of compounds. The reaction is unique in that a nitration is carried out under neutral or alkaline conditions. Acetone cyanohydrin nitrate may also be used for the nitration of many active methylene compounds.⁸

¹ Rohm and Haas Company, Redstone Arsenal Research Division, Huntsville, Alabama. This research was carried out under Ordnance Contract W-01-021-ORD-334.

² R. F. B. Cox and R. T. Stormont, *Org. Syntheses*, Coll. Vol. 2, 7 (1943).

³ W. D. Emmons and J. P. Freeman, *J. Am. Chem. Soc.*, **77**, 4387 (1955).

⁴ W. D. Emmons, *J. Am. Chem. Soc.*, **76**, 3468 (1954).

⁵ W. J. Chute, G. E. Dunn, J. C. MacKenzie, G. S. Myers, G. N. R. Smart, J. W. Suggitt, and G. F. Wright, *Can. J. Res.*, **26B**, 114 (1948).

⁶ J. H. Robson, *J. Am. Chem. Soc.*, **77**, 107 (1955).

⁷ W. D. Emmons, A. S. Pagano, and T. E. Stevens, *J. Org. Chem.*, **23**, 311 (1958).

⁸ W. D. Emmons and J. P. Freeman, *J. Am. Chem. Soc.*, **77**, 4391 (1955).

NITROSOMETHYLURETHANE

WARNING

Nitrosomethylurethane¹ has been reported to be a potent carcinogen by Druckrey and Preussmann.² These investigators suggest that nitrosomethylurethane be handled with greatest care or, preferably, be replaced whenever possible with *p*-tolylsulfonylmethylnitrosamide,³ which was shown to be practically non-toxic and non-carcinogenic under conditions for which the urethane was toxic and/or carcinogenic.

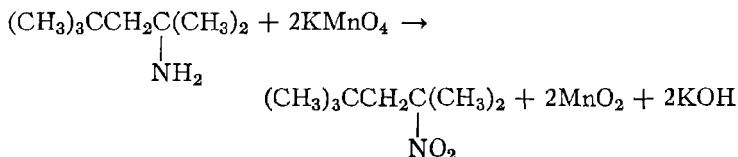
¹ W. W. Hartman and R. Phillips, *Org. Syntheses*, Coll. Vol. 2, 464 (1943).

² H. Druckrey and R. Preussmann, *Nature*, **195**, 1111 (1962).

³ Th. J. DeBoer and H. J. Backer, *Org. Syntheses*, Coll. Vol. 4, 943, 250 (1963).

4-NITRO-2,2,4-TRIMETHYLPENTANE

(Pentane, 2,2,4-trimethyl-4-nitro-)

Submitted by NATHAN KORNBLUM and WILLARD J. JONES.¹

Checked by WILLIAM G. DAUBEN and PAUL R. RESNICK.

1. Procedure

A solution of 25.8 g. (0.20 mole) of 4-amino-2,2,4-trimethylpentane (*tert*-octylamine) (Note 1) in 500 ml. of c.p. acetone is placed in a 1-l. three-necked flask equipped with a "Tru-Bore" stirrer and a thermometer and is diluted with a solution of 30 g. of magnesium sulfate (Note 2) in 125 ml. of water. Potassium permanganate (190 g., 1.20 moles) is added to the well-stirred reaction mixture in small portions over a period of about 30 minutes (Note 3). During the addition the temperature of the mixture is maintained at 25–30° (Note 4), and the mixture is stirred for an additional 48 hours at this same temperature (Note 5). The reaction mixture is stirred under water-aspirator vacuum at an internal temperature of about 30° until most of the acetone is removed (Note 6). The resulting viscous mixture is steam-distilled; approximately 500 ml. of water and a pale-blue organic layer are collected. The distillate is extracted with pentane, the extract is dried over anhydrous sodium sulfate, and the pentane is removed by distillation at atmospheric pressure. The residue is distilled through a column (Note 7) at reduced pressure to give 22–26 g. (69–82%) of colorless 4-nitro-2,2,4-trimethylpentane, b.p. 53–54°/3 mm., n_D^{28} 1.4314, m.p. 23.5–23.7°.

2. Notes

1. The *tert*-octylamine employed was redistilled commercial-grade material, b.p. 140°/760 mm., n_D^{20} 1.4240.

2. The magnesium sulfate was purified dried powder of J. T. Baker Chemical Co. This is approximately 70% magnesium sulfate and 30% water.

3. Good agitation prevents the permanganate from caking on the bottom of the flask. The formation of a cake results in local overheating and consumption of the permanganate as mentioned in Note 4.

4. If a constant-temperature bath is not available, a bucket of water, initially at 25°, serves to dissipate the heat of reaction. At higher temperatures the potassium permanganate is rapidly consumed, presumably by reaction with the acetone.

5. At the end of the reaction time there was no unreacted amine as shown by the following test: A 10-ml. aliquot was filtered through "Supercel" to remove the manganese dioxide, and the filtrate was added to a mixture of 25 ml. of benzene and 25 ml. of water. Extraction of the benzene layer with 10% hydrochloric acid, followed by the addition of sodium hydroxide, gave no oil layer or characteristic odor of the free amine.

6. If agitation becomes difficult during the concentration, 100 ml. of water can be added to give a more fluid mixture.

7. A 60-cm. x 1-cm. externally heated column packed with 4-mm. glass helices and equipped with a total-reflux variable take-off head was used.

3. Methods of Preparation

The procedure described is that of Kornblum, Clutter, and Jones.² 4-Nitro-2,2,4-trimethylpentane has been prepared previously, in low yield, by allowing isoöctane to react with concentrated nitric acid in a sealed tube at elevated temperature.³

4. Merits of the Preparation

This is a general method of preparing trialkylnitromethanes from the corresponding (trialkylmethyl)amines.^{2,4} Table I lists

TABLE I

SYNTHESIS OF TRIALKYLNITROMETHANES, R_3CNO_2

Nitro Compound	Yield, %
2-iNtro-2-methylpropane ^a	83
2-Nitro-2,3-dimethylbutane	71
2-Nitro-2,4-dimethylpentane	82
1-Nitro-1-methylcyclopentane	72
1-Nitro-1-methylcyclohexane	73
1-Nitro-1,4-dimethylcyclohexane	70
1,8-Dinitro- <i>p</i> -menthane	61

^a This oxidation was carried out in water.

seven prepared in this way. The procedure is simple and reliable, and the yields of product are high. Other methods give mixtures of products and low yields of nitro compounds and are inconvenient to perform.

¹ Department of Chemistry, Purdue University, West Lafayette, Indiana. This research was supported by the United States Air Force under Contract No. AF 18(600)-310 monitored by the Office of Scientific Research, Air Research and Development Command.

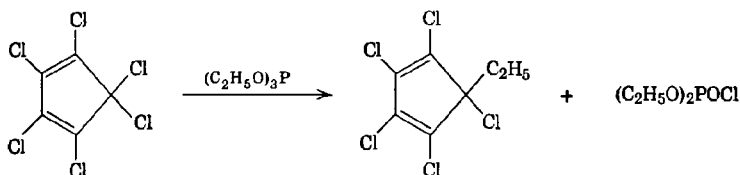
² N. Kornblum, R. J. Clutter, and W. J. Jones, *J. Am. Chem. Soc.*, **78**, 4003 (1956).

³ S. S. Nametkin and K. S. Zabrodina, *Doklady Akad. Nauk SSSR*, **75**, 395 (1950) [*C. A.*, **45**, 6998 (1951)].

⁴ N. Kornblum, *Org. Reactions*, **12**, 101 (1962).

1,2,3,4,5-PENTACHLORO-5-ETHYLCYCLOPENTADIENE

(Cyclopentadiene, 1,2,3,4,5-pentachloro-5-ethyl-)

Submitted by V. MARK, R. E. WANN, and H. C. GODT, JR.¹Checked by WILLIAM E. PARHAM, WAYLAND E. NOLAND,
and G. PAUL RICHTER.**1. Procedure**

A solution of 183 g. (1.10 moles) of triethyl phosphite (Note 1) in 200 ml. of petroleum ether (b.p. 30–60°) is added to a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, a dropping funnel, and an air condenser; the open end of the condenser is connected to a drying tube filled with calcium sulfate or calcium chloride. The flask is immersed in a freezing mixture of sodium chloride and ice, and the stirrer is started. When the temperature of the phosphite solution reaches 0°, a solution of 273 g. (1.00 mole) of hexachlorocyclopentadiene (Note 2) in 100 ml. of petroleum ether (b.p. 30–60°) is added through the dropping funnel at such a rate that the temperature remains between 0° and 10°. The addition requires about 4–6 hours. After the addition is complete, the freezing mixture is removed, and the brown, clear solution is allowed to warm up to room temperature.

The air condenser is replaced by an efficient water condenser set downward for steam distillation. One liter of water is added in one portion to the stirred reaction mixture, and stirring is continued for 30 minutes (Note 3). The dropping funnel is replaced by a steam-inlet tube reaching into the liquid, and steam is passed

through the mixture until first the petroleum ether, then, separately, the ethylpentachlorocyclopentadiene is completely removed. The diene is separated from the steam distillate as a pale-yellow heavy oil. The aqueous phase of the steam distillate is extracted with petroleum ether, and the extract is combined with the diene and dried over calcium sulfate (Note 4). The petroleum ether is removed by evaporation on a steam bath or through a water aspirator at room temperature, leaving 245–257 g. (92–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene as a pale-yellow oil, n_D^{25} 1.5387–1.5400. The diene can be distilled without appreciably lowering the yield; b.p. 51–53°/0.2 mm.; n_D^{25} 1.5398.

2. Notes

1. Triethyl phosphite can be obtained from Virginia Carolina Chemical Corp., Eastman Kodak Co., Aldrich Chemical Co., K and K Laboratories, and Matheson, Coleman and Bell. The presence of dialkyl hydrogen phosphite or trialkyl phosphate is not deleterious, but a correction for assay is required. Fractionation readily separates triethyl phosphite (b.p. 48–49°/11 mm.) from diethyl hydrogen phosphite (b.p. 72°/11 mm.) and triethyl phosphate (b.p. 90°/10 mm.). The presence of amines and amine hydrochlorides may seriously interfere with the alkylation, especially in the case of trimethyl phosphite (see Table I). The checkers redistilled triethyl phosphite obtained from Matheson, Coleman and Bell.

2. A commercial product obtained from Matheson, Coleman and Bell was used.

3. Water hydrolyzes diethyl phosphorochloridate [chlorodiethoxyphosphorus(V) oxide] readily but does not affect the diene. Alternatively, the reaction mixture can be processed by fractionation. Evaporation of the petroleum ether and fractionation of the residue through a 25-cm. x 2.2-cm. column of glass helices yields 170 g. (98.5%) of diethyl phosphorochloridate, b.p. 34–36°/0.2 mm., n_D^{25} 1.4210–1.4250 (the refractive index indicates that it contains 5–10% of the title compound), and 240–255 g. (90–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene, b.p. 51–53°/0.2 mm., n_D^{25} 1.5398.

The reaction mixture can also be processed by chromatography. The crude reaction mixture is poured on a 90-cm. x 4.5-cm. column of alumina (e.g., Fisher "adsorption grade") and eluted with about 2 l. of technical-grade pentane. This yields a pale-yellow solution that is free of diethyl phosphorochloridate. Evaporation of the pentane gives 240–255 g. (90–96%) of 1,2,3,4,5-pentachloro-5-ethylcyclopentadiene.

4. Calcium chloride or sodium sulfate can also be used.

3. Methods of Preparation

1,2,3,4,5-Pentachloro-5-ethylcyclopentadiene has been prepared only by the present procedure.²

4. Merits of the Preparation

5-Alkyl-1,2,3,4,5-pentachlorocyclopentadienes are a novel class of compounds.² The alkylation of hexachlorocyclopentadiene by trialkyl phosphites is a synthetic procedure of considerable scope (Table I) and represents a new method of forming carbon-to-carbon bonds. The products, 5-alkylpentachlorocyclopentadi-

TABLE I

SYNTHESIS OF 5-ALKYLPENTACHLOROCYCLOPENTADIENES, RC_5Cl_5

<i>R</i> ^a	Temperature, °C. ^b	B.P., °C./mm.	n_D^{25}	% Yield
Methyl	20–22	45–47/0.3	1.5465	89
Isopropyl	2–5	67–68/0.4	1.5397	95
Butyl	5–10	72–74/0.3	1.5270	84
Isobutyl	5–10	73–75/0.4	1.5254	72
<i>sec</i> -Butyl	20–25	90–92/0.7	1.5370	89
2-Ethylhexyl	5–10	105–107/0.3	1.5172	90
Dodecyl	5–10	130–135/0.2	1.5043	78
Allyl	20–22	63–65/0.5	1.5450	75
Methallyl	25–40	80–83/0.5	1.5385	80

^a All the trialkyl phosphites required for the preparations listed are available from the suppliers mentioned in Note 1.

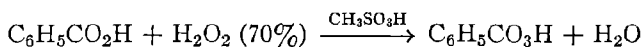
^b Temperature range during the addition period.

enes, show the manifold reactions of the parent chlorocarbon and undergo a variety of substitution and addition reactions, including Diels-Alder reactions.

¹ Monsanto Chemical Co., Agricultural Chemicals Division, St. Louis, Missouri.

² V. Mark, *Tetrahedron Letters*, 1961, 296.

PEROXYBENZOIC ACID



Submitted by LEONARD S. SILBERT, ELAINE SIEGEL, and DANIEL SWERN.¹

Checked by A. S. PAGANO and W. D. EMMONS.

1. Procedure

Caution! All reactions in which 50% or more concentrated hydrogen peroxide is employed must be conducted behind a safety shield. Beakers are recommended as reaction vessels to permit rapid escape of gas and avoidance of pressure build-up in the event of a rapid decomposition.

Twenty-two grams (0.45 mole) of 70% hydrogen peroxide (Note 1) is added dropwise with efficient agitation to a slurry or partial solution of 36.6 g. (0.30 mole) of benzoic acid (Note 2) in 86.5 g. (0.90 mole) of methanesulfonic acid (Note 3) in a 500-ml. tall-form beaker. The reaction temperature is maintained at 25–30° by means of an ice-water bath. The reaction is exothermic during the hydrogen peroxide addition, which requires approximately 30 minutes. During this period the benzoic acid completely dissolves.

The solution is stirred for an additional 2 hours and is then cooled to 15°. Fifty grams of chopped ice and 75 ml. of ice-cold saturated ammonium sulfate solution are cautiously added in sequence while the temperature is maintained below 25° during the dilution (Note 4). The contents of the beaker are transferred to a separatory funnel, and the peroxybenzoic acid solution is

extracted with three 50-ml. portions of benzene at room temperature (Note 5). The aqueous layer is discarded, and the combined benzene extracts are washed twice with 15 ml. of cold saturated ammonium sulfate solution to ensure complete removal of methanesulfonic acid and hydrogen peroxide, dried over anhydrous sodium sulfate, and filtered. Iodometric titration of an aliquot of the benzene solution (Note 6) indicates that the conversion of benzoic to peroxybenzoic acid is 85–90%. This solution can be used directly for epoxidation or other oxidation reactions without further treatment (Note 7).

2. Notes

1. Hydrogen peroxide of this concentration can be obtained from various commercial sources. The submitters have also used 50% and 95% hydrogen peroxide instead of the 70% concentration. With 50% hydrogen peroxide, conversion to peroxybenzoic acid is only about 75%. With 95% peroxide, the reaction proceeds more rapidly and is slightly more exothermic, and conversions of benzoic acid to peroxybenzoic acid are about 90–95% instead of 85–90%. Little advantage is seen in using the more concentrated hydrogen peroxide in the preparation of peroxybenzoic acid except when a high yield of pure crystalline material is needed (Note 7).

2. Benzoic acid of analytical reagent grade is used.

3. Methanesulfonic acid, Eastman Chemicals, practical grade, is satisfactory.

4. Dilution of the methanesulfonic acid is exothermic. Since peroxybenzoic acid has an appreciable solubility in aqueous methanesulfonic acid, dilution and washing are conducted with minimal quantities of saturated ammonium sulfate solution.

5. In the first extraction, 90% of the available peroxybenzoic acid is extracted. The second extraction removes 7%, and the third 2%. The first benzene extract is an approximately 40% solution of peroxybenzoic acid (2.8*M*).

6. A 1-ml. or 2-ml. aliquot of the benzene solution of peroxybenzoic acid is pipetted into an iodine flask, the walls of the flask are rinsed with a small quantity of chloroform, and 15 ml. of

acetic acid is added. Two milliliters of a saturated aqueous solution of analytical reagent grade sodium iodide is added. After a reaction period of about 5 minutes, 50-75 ml. of water is added, and the liberated iodine is titrated with 0.1N sodium thiosulfate solution (starch indicator). One milliliter of 0.1N sodium thiosulfate is equivalent to 0.00691 g. of peroxybenzoic acid.

The analytical method described is also used in following the consumption of peroxybenzoic acid or other peroxy acids during an oxidation reaction; it has also been used in determining the conversion of other carboxylic acids to peroxy acids when solvent extraction has been used in the isolation.

7. If a solvent other than benzene *must* be used in an oxidation reaction, peroxybenzoic acid can be isolated by evaporation of the benzene in an evaporating dish in the hood under a stream of nitrogen gas, or preferably in a rotary evaporator. Evaporation of the solvent from the peroxybenzoic acid solution is preferably conducted as rapidly as possible from a water bath at a temperature below 30°. *Caution! This operation must be carried out behind a good shield. A heavy explosion once occurred during such evaporation of a chloroform solution of perbenzoic acid.*⁷ Owing to the volatility of peroxybenzoic acid, some is lost during solvent evaporation; overall recovery of peroxy acid is 70-90%. The crude peroxybenzoic acid obtained as a residue is a pale-yellow mushy solid or liquid if it still contains traces of benzene. The peroxy acid should be stored in a refrigerator if it is not used immediately.

Analytically pure solid peroxybenzoic acid decomposes at the rate of about 2-3% per day at room temperature, but it can be stored for long periods in a refrigerator without significant loss of active oxygen. Crude preparations lose active oxygen more rapidly. Pure peroxybenzoic acid can be obtained readily from peroxybenzoic acid of 90-95% purity by crystallization at -20° from *olefin-free* 3:1 petroleum ether/diethyl ether cosolvent. About 4.5 ml. per gram of crude peroxy acid is needed, and the solution should be seeded at about 5°. From 15 g. of crude peroxy acid, 9-10 g. of the pure acid, m.p. 41-42°, is obtained as long white needles. To obtain reaction products containing

90–95% peroxybenzoic acid, 95% hydrogen peroxide must be used in the preparation.

3. Methods of Preparation

Numerous methods of preparing peroxy acids are described in the literature,^{2,3} and many of them have been applied to the synthesis of peroxybenzoic acid. A common way of preparing it has been by the action of sodium methoxide on benzoyl peroxide followed by acidification.³ The present method is adapted from one in a recent publication.⁴

4. Merits of the Preparation

The present procedure for peroxybenzoic acid is easier and more reliable than earlier ones. Thus that in an earlier volume of *Organic Syntheses*³ has been found by the submitters to be difficult to reproduce, and yields are frequently low. The modified procedure of Kolthoff, Lee, and Mairs⁵ is an improvement, but it is tedious and indirect.

There are other methods for converting aliphatic acids directly to peroxy acids, but this is the first that converts aromatic acids directly to peroxy acids. With suitable modifications it is applicable to a wide variety of aliphatic and aromatic peroxy acids.⁴ The methyl ester may be used in place of highly insoluble acids. Water-insoluble peroxy acids such as *p*-nitroperoxybenzoic acid (an outstanding epoxidizing agent⁶), *p*-*tert*-butylperoxybenzoic acid, and peroxysearic acid require 90–95% hydrogen peroxide for best results; the procedure is essentially the same *except that greater precautions are necessary with hydrogen peroxide of such high strength*.⁴

¹ Eastern Regional Research Laboratory, Philadelphia 18, Pennsylvania.

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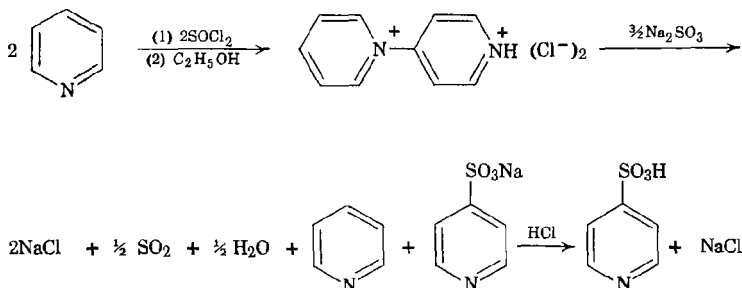
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⁷ P. Westerhof, private communication.

4-PYRIDINESULFONIC ACID



Submitted by RUSSELL F. EVANS,^{1,2} HERBERT C. BROWN,¹
and H. C. VAN DER PLAS.³

Checked by JAMES CASON and TAYSIR JAOUNI.

1. Procedure

A. *N*-(4-Pyridyl)pyridinium chloride hydrochloride. In a 2-l. round-bottomed flask equipped with a ground joint (Note 2) is placed 395 g. (5.00 moles) of dry pyridine (Note 3). As this flask is cooled by swirling in a bath of cold water (Note 4), there is added during a few minutes 1190 g. (10.0 moles) of a good commercial grade of thionyl chloride (Note 1). After completion of the addition, the flask is protected by a drying tube, and the reaction mixture is allowed to stand at room temperature under a hood for 3 days. During this period, the color of the mixture changes from deep yellow through brown to black.

The flask is fitted with a Claisen head, and excess thionyl chloride is distilled at reduced pressure (water pump) and collected in a receiver cooled in a mixture of dry ice and acetone (Note 5). The flask is heated with a water bath that is slowly raised from room temperature to about 90°, then held at that temperature until no more distillation occurs and a black residue remains.

The black residue is cooled to 0°, and 100 ml. of ice-cold ethanol is added very cautiously to react with residual thionyl

chloride. An additional 400 ml. of ice-cold ethanol is added, and the solid mass left at the bottom of the flask is broken up with the aid of a rod (Note 2). The resultant light-brown powder is collected by suction filtration, preferably on a sintered glass funnel, and washed with five 150-ml. portions of ethanol. The yield of crude N-(4-pyridyl)pyridinium chloride hydrochloride is 230–257 g. (40–45%). This product is very deliquescent and should be used immediately or stored over phosphorus pentoxide.

B. *4-Pyridinesulfonic acid*. A 115-g. (0.50 mole) quantity of N-(4-pyridyl)pyridinium chloride hydrochloride is dissolved in 750 ml. of water in a 2-l. round-bottomed flask, and 378 g. (1.50 moles) of solid sodium sulfite heptahydrate is added cautiously. After the evolution of sulfur dioxide has ceased, the solution is gently heated under reflux in a nitrogen atmosphere for 24 hours. After slight cooling, 20 g. of charcoal is added to the mixture, and it is heated under reflux for an additional hour. The resultant mixture is filtered through a fluted paper, the filtrate is evaporated to dryness on a steam bath under reduced pressure, and the residue is air-dried at 100–110° (Note 6). This solid is now continuously extracted with absolute ethanol for 24 hours in a Soxhlet apparatus. The alcohol is distilled from the extract on a steam bath, and the crude sodium 4-pyridinesulfonate is dissolved in about 160 ml. of hot water. After 320 ml. of 12*N* hydrochloric acid has been added with mixing, the solution is cooled to room temperature. The precipitate of sodium chloride is filtered, and the filtrate is evaporated to dryness under reduced pressure on a steam bath. Crystallization of the residue from 600 ml. of 70% aqueous ethanol yields 27–30 g. of colorless crystals of 4-pyridinesulfonic acid, m.p. 313–315° (dec.). Concentration of the mother liquor affords about 10 g. of additional product which is less pure. The total yield is 36–40 g. (45–50%) (Note 7). Recrystallization from 70% aqueous ethanol affords a purer specimen, m.p. 317–318° (dec.). (Note 8).

2. Notes

1. Although N-(4-pyridyl)pyridinium chloride hydrochloride is formed by reaction of pyridine with thionyl chloride, followed

chloroform and the chloroform distilled from the steam bath. The checkers used a vacuum oven for drying.

7. The submitters report yields in the range 63–70%.

8. Because the sulfonic acid melts with decomposition, the value observed for the melting point is highly dependent on the rate of heating of the sample.^{9–12}

3. Methods of Preparation

The preparation of N-(4-pyridyl)pyridinium chloride hydrochloride follows the procedure of Koenigs and Greiner,⁶ while the preparation of the sulfonic acid is a modification of a patent procedure.¹³

4-Pyridinesulfonic acid has been prepared by oxidation of 4-pyridinethiol with hydrogen peroxide in barium hydroxide solution,⁹ with hydrogen peroxide in glacial acetic acid,¹⁰ with nitric acid-chlorine or nitric acid-chlorine-hydrochloric acid mixtures,¹¹ and with nitric acid alone.^{10,12,14} The latter reaction gives a mixture of 4-pyridinesulfonic acid and other products, e.g., di-4-pyridyl disulfide dinitrate, and this has led to some confusion in the literature.^{10–12,14}

Sodium 4-pyridinesulfonate has been obtained from the oxidation of 4-pyridinethiol with hydrogen peroxide in sodium hydroxide solution,¹⁵ and from the reaction of 4-chloropyridine with aqueous sodium sulfite.¹⁶ The salt has been converted to the free acid by treatment with a cation-exchange resin^{10,11} or with sulfuric acid.¹¹

4. Merits of the Preparation

This is the most convenient preparation of 4-pyridinesulfonic acid, a useful intermediate for the synthesis of various pyridine derivatives

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³ Landbouwhogeschool, Laboratorium voor Organische Chemie, Wageningen, Holland

⁴ F. Krohnke, *Angew. Chem.*, **65**, 623 (1953)

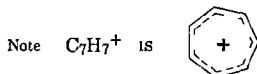
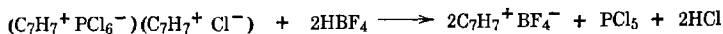
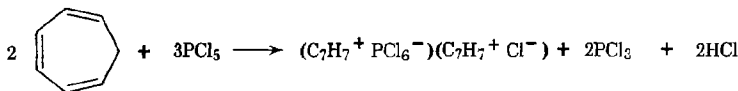
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TROPYLIUM FLUOBORATE

(Cycloheptatrienocarbonium fluoborate)

Submitted by KENNETH CONROW¹

Checked by D W WILEY and B C McKUSICK

1. Procedure

A suspension of 100 g (0.48 mole, 33% excess) of phosphorus pentachloride in 800 ml of carbon tetrachloride is prepared in a 1-l flask equipped with an efficient stirrer and an exit valve for the hydrogen chloride that is evolved (Note 1). Tropilidene (cycloheptatriene, 24.2 g of 91% material, 0.24 mole) (Note 2)

is added all at once, and the mixture is stirred for 3 hours at room temperature (Note 3).

Absolute ethanol (400 ml.) is vigorously stirred in a 1-l. wide-necked Erlenmeyer flask immersed in an ice bath (Note 4). The tropylium hexachlorophosphate-tropylium chloride double salt ² is separated from the reaction mixture by suction filtration, washed briefly with fresh carbon tetrachloride, and transferred as rapidly as possible into the cold, well-stirred ethanol (Note 5). The salt dissolves rapidly and exothermally to give a reddish solution. Fifty milliliters (0.39 mole) of 50% aqueous fluoboric acid is added rapidly to the cold stirred solution (Note 6). The dense white precipitate of tropylium fluoborate that forms is separated by suction filtration, washed with a little cold ethanol and with ether, and air-dried at room temperature (Note 7); weight 34-38 g. (80-89%); decomposition point about 200°; $\lambda_{\max}^{0.1N \text{ HCl}}$ 218 m μ (log ϵ 4.70), 274 m μ (log ϵ 3.61). The product is 98-100% pure (Notes 8 and 9).

2. Notes

1. The use of a flask just large enough to hold the reaction mixture obviates the necessity for an inert atmosphere, for the evolving hydrogen chloride soon displaces the small amount of air over the reaction mixture.

2. Cycloheptatriene containing 9% toluene is available from the Shell Chemical Company, New York. Less pure cycloheptatriene, obtained by pyrolysis of bicycloheptadiene followed by a crude distillation, has been used successfully in this preparation. The quantity of the tropilidene/toluene mixture is adjusted in accord with its purity as estimated by vapor-phase chromatography on didecyl phthalate.

3. The mixture thickens rapidly. After about an hour, even an efficient stirrer often fails to stir the whole mixture, but after a time the mixture thins again and the reaction is completed without incident.

4. Stirring is most conveniently accomplished with a magnetic stirrer. A large plastic bucket is used to contain the ice used for cooling.

5. Exposure of this salt to the atmosphere causes discoloration that may persist in the final product. A slight discoloration at this stage does not appear to affect the quality of the final product. A rubber dam is helpful on days of high humidity.

6. Use of perchloric acid gives the perchlorate. However, the perchlorate is so dangerously explosive that its use should be avoided.³

7. Additional salt is precipitated by the addition of ether to the ethanolic filtrate, but the quantity is so small that this treatment is not worth while.

8. The product may be crystallized from a large volume of ethyl acetate or from acetonitrile-ethyl acetate. However, there is little reason to do this, for losses are heavy and the purity, as measured by ultraviolet spectroscopy, is hardly affected.

9. In a variation of this procedure that gives a nearly quantitative yield of good material, the intermediate salt is dissolved in 250 ml. of glacial acetic acid in a 2-l. beaker, and 100 g. of 50% fluoboric acid is added with stirring. When the evolution of gas has stopped, 1 l. of ethyl acetate is added to precipitate tropylium fluoborate. The fluoborate is separated by filtration, washed successively with ethyl acetate and ether, and dried in an oven at 40°.⁴

3. Methods of Preparation

This method is a modification of the method originally published by Kursanov and Vol'pin.⁵ Tropylium salts have also been prepared by bromination-dehydrobromination of tropilidene,⁶ and by the hydride-exchange reaction between tropilidene and triphenylmethyl carbonium ion.⁷

4. Merits of the Preparation

Tropylium salts are starting materials for the preparation of a wide range of substituted tropilidenes. The fluoborate is the salt of choice for work involving the tropylium ion because it is indefinitely stable, non-hygroscopic, and, unlike the perchlorate, non-explosive. Its preparation by this method avoids the use of

triphenyl carbinol, which is an unnecessarily expensive reagent in the quantities required for tropylium ion preparation

¹ Department of Chemistry, Kansas State University, Manhattan, Kansas

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SUBJECT INDEX

(This index comprises material from Volumes 40-43 only, for previous volumes see Collective Volumes 1, 2, 3, and 4)

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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

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Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the **range** of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point **range** should be reported, and for each liquid product the **range** of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

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Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

Organic Syntheses was founded by Roger Adams, Hans T. Clarke, James B. Conant, and Oliver Kamm in 1921. At that time few compounds could be bought and, in the words of the preface in Volume 1, "the preparation of materials for research, always time consuming and annoying," was "made increasingly so by the inexactness of the published information, which so often omits essential details." *Organic Syntheses* was founded primarily to provide research chemists with detailed, reproducible "methods of preparation of some of the most needed organic chemical reagents," and it is a measure of the progress chemical technology has made since 1921 that, when Volume 1 was published, allyl alcohol, furfural, and trimethylamine were among the compounds for which good directions were urgently needed by research chemists. The procedures of *Organic Syntheses* also served as models for carrying out various types of reactions, but that was a secondary aim in the early years.

Although there are some 1400 procedures in the 43 volumes that have appeared annually since the founding, there is no sign that the supply of suitable procedures is running out. However, there has been a gradual change in emphasis in the types published. This change has come about because the number of commercially available compounds has risen steadily during the 43 years of *Organic Syntheses'* history and is now in the thousands. As a result, the need for procedures describing specific compounds has decreased relative to the need for those illustrating general reactions. This trend is particularly evident in recent volumes of *Organic Syntheses*, which have emphasized examples of relatively new reactions of general usefulness.

In the present volume, easily three-fourths of the preparations fall into this class. Thus the preparation of docosanedioic acid (p. 34) demonstrates how acylation of an enamine can be used to prepare long-chain acids. The preparation of N-nitromorpholine

(p. 83) shows a general way of putting a nitro group on the nitrogen of secondary amines. Three general types of cycloaddition are illustrated: addition of an allene to an alkene (dimethyl 3-methylenecyclobutane-1,2-dicarboxylate, p. 27), addition of a fluoroölefin to an alkene (1-chloro-1,4,4-trifluorobutadiene, p. 17), and addition of a chlorophosphine to a 1,3-diene (3-methyl-1-phenyl-1-phospha-3-cyclopentene 1-oxide, p. 73). Improved versions of the Schiemann reaction (1-bromo-2-fluorobenzene, p. 12) and the Hunsdiecker reaction (bromocyclopropane, p. 9) exemplify modern methods of introducing halogen into molecules. 1,4-Dihydrobenzoic acid (p. 22) illustrates the Birch reduction.

The chief value of several procedures lies in current research interest in the products. Tropylium fluoborate (p. 101) is a good example.

I appreciate the help in assembling this volume that I received from Dr. Norman G. Fisher, who advised me on nomenclature, Dr. Wallace Copeland, who checked most of the references, and Mrs. Irene Dutton, who typed the manuscript and checked proof.

BLAINE C. MCKUSICK

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